Clinical profile and outcome of extranodal non-Hodgkin's Lymphoma : Experience of a regional cancer centre in the South Asian subcontinent

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government lowered the minimum ethanol concentration for the definition of drunk driving, with the threshhold breath alchohol concentration (BRAC) of 0.15 mg/L. The aim of this study was to measure BRAC in Japanese outpatients treated with P or D and to assess intoxication according to this standard.
Patients and methods: Japanese patients receiving P or D for treatment of non-small cell lung cancer, breast cancer, or ovarian cancer gave written informed consent for breath samples to be taken. Breath samples were measured three times immediately following the infusion of P or D via ethyl alcohol detector Alscan CA-2000. The mean value of BRAC was recorded. In cases where BRAC was detected, BRAC was re-measured 30 minutes after the initial measurement. Symptoms of alcohol intoxication during chemotherapy were assessed by a patient questionnaire.
Results: Fifty patients were enrolled through August to December 2003. Patient characteristics were as follows: male/female: 12/38, median age: 55 (range, 34-78), breast/lung/ovarian cancer: 23/15/12, P/D treatment: 34/16, respectively. The mean total doses of P or D were 181 mg (range, 108-300) and 53 mg (30-100), respectively. BRAC were detected in 20 patients (59%) with P, and no D patients. In 4 of 6 BRAC re-measured pts, BRAC became undetectable after 30 minutes. There was no correlation between the doses of P and BRAC (r=0.249; 95% C.I.: -0.097-0.542). Five of 20 pts felt drunkenness.
Conclusion: Clinicians should recognize the potential for alcohol intoxication with paclitaxel administration. Patients should not be allowed to drive for at least 30 minutes after receiving paclitaxel.

569P The prognostic Importance of Venous Thromboembolism (VT) in cancer patients and its relationship with the levels of factor VIII and Vascular Endothelial Growth Factor (VEGF)

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Venous thromboembolism (VT) increases mortality and morbidity in cancer patients. We prospectively studied the prognostic value of VT in patients with various cancers. In addition, the relationship between serum VEGF or plasma factor VIII level or erythrocyte sedimentation rate (ESR) and the prognosis of cancer patients were also evaluated. Eighty two cancer patients who had locally advanced or metastatic disease were included in this study. Thirty-one patients with VT were consequtively included in this trial from September 2001 to March 2004 in a single center. Fifty-one matched-paired patients without VT were prospectively selected as a control group in the same period. Criteria for control patients were having similar malignancy, stage, metastasis, performance status, age group (± 5 years) and gender. Factor VIII levels and ESR were significantly higher in the group having VT as compered with control patients (p = 0.031 and 0.001, respectively) whereas mean serum VEGF levels were similar in two groups (p = 0.190). The median survival was significantly shorter in patients having higher levels of VEGF in the patients with VT (p=0.005). However, there was no significant difference between the main groups for overall survival (p=0.075).
Conclusion: There was a worse prognosis trend for cancer patients with VT. Plasma factor VIII level and ESR had prognostic value in patients with VT. Cancer patients with VT having higher VEGF levels seem to have poorer prognosis.

570P PIPOH: A new tool for use in clinical practice guidelines adaptation

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Clinical practice guidelines (CPGs) aim to promote an evidence-based approach to healthcare. A rigorous development process is essential to guarantee their scientific validity and quality, but this is costly and time consuming. Adaptation of CPGs for local use could reduce the costs and time, and also avoid unnecessary duplication of effort. In the setting of a France-Quebec collaboration we have developed a detailed process for the adaptation of CPGs in oncology. The five major steps in the adaptation process are: definition of the clinical question; search for appropriate CPGs; CPG selection; assessment of CPGs for internal validity and appropriateness for the context of use; and adoption or adaptation of the recommendations from one or more CPGs. We have developed a tool - PIPOH - that can be used in defining the clinical question, the search strategy, and the criteria for the selection and evaluation of the CPGs. PIPOH consists of five domains: Population, Interventions, Professionals, Outcomes, Healthcare setting. Each domain includes a list of selectable terms so that the working group can decide the level of detail necessary to define the scope of the CPG to be adapted. For example, within the domain Population, there are terms related to the type of cancer, as well as others describing the patient. The Intervention domain includes terms such as screening, diagnosis, treatment, support, follow up, and others. The Professionals domain concerns the target users of the CPG, such as clinicians or other stakeholders. The Outcome domain includes terms such as tumour response, survival, quality of life, safety. The final domain describes the Healthcare setting to which the CPG applies (primary care, at-home hospitalisation, etc). Thus PIPOH will aid to select and evaluate appropriate and pertinent CPGs for adaptation. PIPOH complements the AGREE instrument, which is used in the adaptation process to assess the methodological quality of the CPGs. Pilot testing of the adaptation process, including the PIPOH tool, is under way in Quebec and in France.

HEMATOLOGICAL MALIGNANCIES

571O Results of Autologous Stem Cell Transplantation for Multiple Myeloma conducted from 1989-2003 in Austria

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Background: Two prospective randomized trials (IFM 90 and MRC) and a meta-analysis of 4 randomized trials showed superiority of high-dose therapy + autologous stem-cell transplantion (ASCT) over conventional treatment, although a recent US intergroup trial was unable to confirm a benefit. Double (DT) vs. single transplantation (ST) produced a significant prolongation of overall survival (OS) in a French trial (IFM 94), and improvement of EFS in 2 trials, and no effect in 1 trial. Here we report the results of ASCT in all patients (> 99.5%) with MM treated in Austria.
Patient and Methods: Data on 324 patients treated with ASCT from 1989 onwards reported to the Austrian SCT Registry have retrospectively been analysed. Median age of patients was 55.6 years (range 24.6 - 70.7 years). Source of stem cells was PB in 317 patients, while only 7 patients received BM derived stem cells. Hundert-and-seventy patients were treated with ST and 98 with DT, while all other patients received >2 autografts. Total body irradiation (TBI) was given to 33 of 136 evaluable patients. All but one patient were evaluable for survival, and 265 patients were evaluable for response.
Results: A CR by conventional criteria (without proof of negative immunofixation) was achieved in 37% and a PR in 53% of patients, yielding an OR rate of 90%. Transplant related mortality was 2.5% at 3 months, and median survival 66.5 months at a median follow-up of 14.2 months. DT yielded a significantly longer OS as compared to ST (p< 0.05; survival at 1 year 86% vs. 71%, respectively). There was a tendency for a shorter OS in patients receiving TBI as compared to patients receiving conditioning without TBI (survival 51 months vs. not reached, p=n.s.). Preliminary analysis shows significant prolongation of maintenance duration and OS with interferon maintenance treatment, but final analysis of a matched pair analysis will be presented.
Conclusion: High dose chemotherapy with ASCT revealed a favourable survival (66.5 months) in patients with MM of which only a minority have been treated in clinical trials in Austria. DT and interferon maintenance treatment were associated with a significantly longer survival, while use of TBI was associated with a tendency towards shorter survival.

572O Idiotype specific cellular immune response in multiple myeloma patients as assessed by five different methods

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Background: The idioype (Id) may be regarded as a tumor specific antigen (TSA) in multiple myeloma (MM) and, as such, may be a target for natural and induced Id specific immune responses. In this study, 5 different readout systems ((proliferation assay, ELISPOT, real-time PCR, cytokine flow cytometry (CFC), and cytometric bead array (CBA)) were compared with regard to their ability to detect Id specific T cell responses.
Methods: DNA synthesis and ELISPOT (IFN-γ) were traditional basic methods for monitoring immune responses. In addition CFC was included for phenotypic characterization of the Id specific IFN-γ producing cells, and real-time PCR and CBA were further applied and compared for the detection of Id-induced IFN-γ, IL-2, TNF-α, and IL-5 expression. Five patients with early stage MM from an ongoing Id vaccination study were included. Patients were repeatedly immunized with the autologous Id protein together with the adjuvant cytokine(s) IL-12 alone or a combination of IL-12 and GM-CSF. Id specific cellular immune response was analyzed before vaccination and at 6 time points during 32 week long vaccination period.
Result: A significant correlation was noted between Id specific proliferative T cell response and Id-induced IFN-γ production (ELISPOT) ($p < 0.0001$) as well as between Id-induced IFN-γ gene expression (real-time PCR) and protein production as detected by both ELISPOT ($p < 0.0001$), and CFC ($P < 0.0001$). No significant correlation could be noted between proliferation assay, real-time PCR, and CBA.
Conclusion: The results indicate that various readout systems may correlate at the protein and gene levels but also that multiple analytic tools may be required to fully describe an immune response against weak self antigens such as the Id protein. This information should be considered when designing clinical vaccine trials including immune monitoring.

573O Marked clinical activity of the novel proteasome inhibitor bortezomib in patients with relapsed follicular and mantle cell lymphoma

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Targeting of the ubiquitin proteasome pathway has proven to be a valid approach in the treatment of hematologic malignancies. The proteasome plays a vital role in regulatory proteins that govern cell cycle progression, transcription factor activation & apoptosis. We have administered more than 280 cycles of bortezomib to 39 patients with relapsed or refractory indolent lymphomas, including 4 patients with small lymphocytic lymphoma-CLL type, 15 patients representing all grades of follicular lymphoma, 17 patients with mantle cell lymphoma, and 3 patients with marginal zone lymphoma. Patients were required to sign an informed consent and to have hematologic counts. All but 1 patient had received some form of treatment prior to receiving bortezomib, including CHOP +/- R (57%), CVP +/- R (24%), or some other purine analog-based treatment program (15%), with some patients having received prior high-dose chemotherapy with peripheral blood stem cell transplantation (11%). Patients were treated at a dose of 1.5 mg/m^2 twice weekly for 2 weeks with a 1-week rest period. No grade 4 toxicities were observed. Restaging studies were routinely performed after 2 complete cycles of therapy. One of 4 evaluable patients with small lymphocytic lymphoma had a PR, and the remaining 3 had SD. Seven of 15 evaluable patients with follicular lymphoma achieved a major response, with 2 patients obtaining complete responses. As of May 2004, these responses lasted between 6+ and 10+ months each. Two evaluable patients with marginal zone lymphoma achieved a PR after 2 cycles of therapy, lasting 3+ and 6+ months each. Of 11 evaluable patients with mantle cell lymphoma, 6 achieved a partial remission (response rate of 55%), with these responses lasting 1+, 2+, 4+, 6, 6+, and 19 months. The patient who attained a PR lasting 19 months was retreated with 4 cycles of bortezomib, and achieved a second PR now lasting 7+ months. One of 4 patients with small lymphocytic lymphoma/CLL responded with a PR. These data support the biological activity of bortezomib in patients with non-Hodgkin's lymphoma. An update on this activity, and the differences between the different NHL subtypes will be discussed.

574O Treatment of new cases of acute promyelocytic leukaemia by arsenic trioxide

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Purpose: We studied the effects of Arsenic Trioxide as first line treatment of new cases of APL and their follow up and also outpatient salvage treatment of relapsed cases by Arsenic trioxide.
Material and methods: we studied 63 new cases of APL diagnosed by morphologic criteria and confirmed by presence of t (15,17).
Our patients were 28 males and 35 females with median age 27±11.98. Patients treated by infusion of 0.15mg/kg/d of Arsenic Trioxide to complete remission by morphologic criteria or till day +60. In patients who complete remission achieved, after 28 days rest, again we began Arsenic Trioxide 0.15mg/kg/d for 28 days as consolidation.
Results: complete remission was achieved in 57 patients (90.5%) and 6 early mortality. Median time to complete remission was 30±6.6 days. Most common cause of mortality was APL maturation syndrome (4 cases)
Most common toxicities during induction phase were, APL maturation syndrome (14.7%), serositis (11.4%) and hepatotoxicity (18%).
88.5% of patients are alive with a median follow up of 12±10.02 months. 11 relapses observed in our patients and complete remission achieved with retreatment by Arsenic trioxide in 8 of them. 6 patients without preceding APL differentiation syndrome treated as outpatient to complete remission without any adverse effect and they are in complete remission now.
Mean survival time of patients by Kaplan-Meier method was 33.91 months (CI95% 30.98-37). Most common cause of death was APL maturation syndrome in 3 patients and relapse in 3 cases.
Conclusion: Arsenic Trioxide is acceptable as first line treatment of APL and its result is comparable to ATRA with chemotherapy. Also it is effective as salvage therapy of relapsed cases after treatment by Arsenic trioxide again and outpatient treatment is possible.

575O Comparison of outcomes in lymphocyte-predomminant (LPHD) and classical Hodgkin's Disease (cHD). Review of three study generations of the German Hodgkin Lymphoma Study Group (GHSG)

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Introduction: PHD differs in pathology and clinical presentation from cHD. The European Task Force on Lymphoma project found that treatment of LPHD patients (pts) using standard Hodgkin disease (HD) protocol can lead to CR in more than 95% of pts. However, survival and freedom from treatment failure (FFTF) are substantially worse in advanced stage pts compared with early stage pts. Since there are no randomized studies, the GHSG reviewed all LPHD-cases registered in the last studies and compared treatment outcome with cHD pts.
Patients and methods: e retrospectively analysed 8597 HD pts treated within the GHSG trials (HD4 to HD12): 401 LPHD pts and 8196 cHD pts. From 401 LPHD pts 43.9% were in clinical stage (CS) I, 33.2% in CS II, 17.7% in CS III and 5.2% in CS IV. Of the 8196 cHD pts analysed, 13.1% were in CS I, 49.9% in CS II, 23.8% in CS III and 13.2% in CS IV. 9% LPHD pts developed B symptoms compared to 39.5% in cHD pts.
Results: 87.1% LPHD pts reached CR/CRu compared to 80.7% cHD pts. 0.4% LPHD pts developed progressive disease (PD) compared to 3.4% cHD. In LPHD pts there were no PD in CS I and CS II, 1.4% LPHD pts in CS III and 4.8% in CS IV developed PD. The relapse rate of LPHD pts was very similar to cHD (6.9%). 4.0% LPHD pts and 8.2% cHD pts died. FFTF rates according to clinical stages in LPHD pts were following: 93% for CS I (median observation time (MOT) 40 months), 88% for CS II (MOT 39 months), 87% for CS III (MOT 44 months) and 70% for CS IV (MOT 43 months). Appropriate OS rates were: 99% for CS I, 95% for CS II, 95% for CS III and 79% for CS IV. Full analysis of data will be presented.
Conclusion: cHD pts present more frequently with advanced stages and B symptoms compared to LPHD pts. FFTF and OS rates for LPHD pts showed significant differences between early and advanced stages. Comparing LPHD and cHD pts we found differences in treatment outcome in respect of CR/CRu, progressive disease and mortality. Surprisingly, there were no differences in terms of relapses. In contrast to previous reports, our data suggest that relapses in LPHD and cHD pts seem to be comparable and not more frequent.

576PD Prognostic factors and outcome in 306 patients with diffuse large B-cell lymphoma (DLBCL)

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Since 70% of pts with DLBCL achieve complete remission and 30-50% of pts are cured, it is important to manage pts according to prognostic factors predicting response to therapy and survival. In this retrospective study, 306 consecutive pts with DLBCL were analyzed for prognostic factors. Median age of pts was 49; 49% and 27% presented with bulky disease and advanced stage, respectively. According to IPI, 15% of pts were in high or high-intermediate risk group. Most common treatment modality was chemotherapy(36%), followed by combination of chemotherapy and radiotherapy (31%). Chemotherapy regimens were containing anthracycline in 94% of pts. During a mean follow-up of 47 months, 82 (27%) pts relapsed and 115 (38%) pts died. The 5-year-overall survival (OS) and 5-year-progression-free survival (PFS) were 60% and 52.7%, respectively. In univariate analysis, adverse prognostic factors for OS were age, B symptoms, bulky disease, poor performance status (PS), elevated LDH, advanced stage, involvement of >1extranodal site, elevated ESR, low serum albumin level, IPI ≥3 and treatment with regimens not containing anthracycline. Response to first-line therapy was also a significant variable predicting OS. B symptoms, involvement of >1 extranodal site, advanced stage, poor PS, elevated ESR, low serum albumin level, elevated LDH, IPI ≥3 and treatment with regimens not containing anthracycline were adverse prognostic factors for PFS. In multivariate analysis of prognostic factors available at time of diagnosis, IPI and treatment with anthracycline-containing regimens were significant variables for PFS and OS; while independent prognostic factors for PFS and OS after completion of therapy were response to first-line therapy and treatment with anthracycline-containing regimens. In relapsed pts, prognostic factors for OS were IPI at relapse and time to treatment failure. When response to salvage therapy was included, prognostic significance of IPI at relapse was replaced with response to salvage therapy. In conclusion, considering the limited benefit from second-line therapies in pts with poor prognostic factors, intensification of first-line therapies before development of resistance or relapse can improve survival rates.

577PD Rituximab and infusional cyclophosphamide, doxorubicin and etoposide (cde) in combination with haart: a safe and highly active regimen in HIV-related non-Hodgkin's lymphomas (NHL)

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The combination of Rituximab plus chemotherapy (ct) is more effective than CT alone in the treatment of high grade NHL With the aim to evaluate the efficacy and activity of combining infusional cde plus Rituximab in HIV-NHL, we started a phase II study using infusional cde (Cyclophosphamide 187.5 mg/m^2/day, Doxorubicin 12.5 mg/m^2/day and Etoposide 60 mg/m^2/day) administered by continuous intravenous infusion for 4 days every 4 weeks and Rituximab 375 mg/m^2 i.v. on day 1. haart was given concomitantly with ct. From June 1998 to December 2002, 74 patients (pts) have been enrolled. The median CD4+ cell count was 161 (range 3-691) and the median performance status was 1 (range 0-3). Seventy per cent of pts had advanced stage (III-IV) disease and 49% had B symptoms. Fifty-two out of 74 pts (70%) achieved a complete remission (cr), 4/74 (5%) had a partial remission and 18 (25%) progressed. Only 7/52 pts (13%) in CR relapsed and 48/74 (65%) are alive. Grade 3-4 neutropenia, anemia and thrombocytopenia were observed in 78%, 32% and 24% of pts respectively. Twenty-six per cent of pts developed bacterial infections during neutropenia. The actuarial overall survival and time to treatment failure (TTF) at 2 years were 62% and 64%, respectively. In a Cox model, Burkitt subtype was significantly associated to a shorter survival in comparison with diffuse large B-cell NHL. Our data show that the combination of Rituximab and cde in hiv-NHL treated concomitantly with HAART is safe, feasible and active. CR rate (70%) and TTF at 2 years (64%) are comparable to those observed in high grade NHL of the general population even if a more aggressive treatment should be evaluated for Burkitt subtype.
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578PD Vaccination of B-cell chronic lymphocytic leucaemia patients with peripheral blood autologous apoptotic leucaemic cells

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Chronic B-cell lymphocytic leukemia (B-CLL) is a heterogenous disorder, it generally follows an indolent clinical course, with most of patients do not requiring any therapeutical intervention for some time from initial diagnosis. Immunotherapy may be an advatageous therapeutical option for these group of patients, because in early stages of the disease the tumour burden is relatively small Our attempt was directed on use of irradiated peripheral blood autologous leukaemic B-CLL cells, as a vaccine in patients with B-CLL. We hypothesized, that apoptotic leukemia cells, specially in presence of BCG vaccine, will induce skin dendritic cells maturation and than their activation following migration to regional lymph nodes. In lymph nodes the dendritic cells may present the processed leukemia antigens to T cells and activate them to CTLs directed against B-CLL cells of the patient. From June 2002 till February 2004 10 untreated B-CLL patients in stage 0 or 1 acc. Rai were included into the study. Patients were vaccinated with autologous irradiated leukaemic cells. Vaccines were administered once a week during first month of therapy, and then every two weeks until 12 doses, sc. In the first two injections the irradiated cells were mixed with viable fresh frozen BCG suspension. The phenotype of peripheral blood leukocytes and lymphocytes was assayed by cytometry before every vaccination and every 3 months after the end of therapy. In one of the patients vaccinated from June 2002 to January 2003 the number of leukocytes and lymphocytes remained on the similar level and in the other one decreased during 18 months observation period. In the patients treated from November 2003 stable disease is observed so far. Most remarkable phenotypic change during vaccination was rise in CD3+CD8+ population of T lymphocytes. CD4/CD8 ratio decreased and populations of monocytes and NK cells normalized after vaccination. No serious treatment-related adverse events were observed. An attempt was made for the first time in CLL patients to use directly of apoptotic B-CLL cells. After 18 months from start of vaccination the patients are in a stable phase of the disease. Further patients are vaccinated and observed now.

579PD The gene Hypermethylated In Cancer (HIC1) is differentially regulated in granulocytic differentiation of myeloid leukaemic cells

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Acute myeloid leukaemia (AML) is characterised by blocked differentiation. To define genes with specific regulatory patterns in AML maturation, we obtained gene profiles with DNA microchip analyses from HL-60 and t(15;17)+ NB-4 leukaemic cell lines. Granulocytic differentiation was induced *in vitro* with all-trans retinoic acid (ATRA), and monocytic differentiation with phorbolester myristate (PMA) over 3-6 days. mRNA extracted from undifferentiated and differentiated leukaemic cells was analysed for gene expression profiles, which were also tested against expression profiles from fresh AML samples to increase the stringency of selecting differentiation-associated genes. During granulocytic differentiation of both leukaemic cell lines, ATRA induced the HIC1 gene to a particularly marked extent. ATRA-induced up-regulation of HIC1 mRNA production was confirmed in quantitative RT-PCR experiments (100x in HL-60, and 1000x in NB-4). In PMA differentiated HL-60 cells no change in HIC1 expression was detectable. An HIC1 expression screen of clinical samples and normal leukocytes showed, that HIC1 mRNA was 200x lower in AML samples (n=62), or in CD34+ progenitor cells (n=3) than in normal granulocytes (n=4). Blocking protein production with cycloheximide (CHX) in cell lines exposed to ATRA demonstrated that HIC1 belongs to the family of "early-response" genes, since HIC1 mRNA up-regulation was not abolished by CHX and thus independent from protein synthesis. In NB-4 cells, we noted HIC1 mRNA superinduction by combining CHX and ATRA. HIC1 mRNA induction by ATRA was reproduced in primary AML cells. In AML blasts from two untreated patients (AML FAB type M2 and M4) cultured *in vitro*, HIC1 mRNA production was induced after 3 days of ATRA by 30x and 60x, respectively. HIC1 has emerged from these experiments as an interesting new candidate gene involved in normal and leukaemic myeloid differentiation. Whilst HIC1

has been described as a candidate tumour suppressor gene, a role of this gene in myeloid differentiation and in the AML differentiation block has so far never been described. Our data provide a first basis to identify HIC1 as a possible molecular target in AML.

580PD Final analysis of a randomized phase I study of the C-RAF kinase inhibitor BAY 43-9006 in patients with acute myeloid leukemia

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Introduction: BAY 43-9006 (BAY) is an orally administered small molecule inhibitor of C-RAF and B-RAF kinases and the receptor tyrosine kinases VEGFR-2, PDGFR-β and flt-3. BAY has broad activity in preclinical models and is currently in phase II and III testing in solid tumors. We performed a *randomized phase I trial of BAY to define the optimal dose and schedule* in patients (pts) with acute myeloid leukemia (AML).
Patients and Methods: Pts with MDS or AML (1 prior regimen, unless elderly or secondary AML at high risk of treatment failure or toxicity) were randomized to either BAY daily × 28 days (continuous) or daily × 14 days followed by a 14 day treatment-free period (intermittent), escalated at 3 dose levels (100, 200 and 400 mg bid orally). Peripheral blood (PB) blasts were assessed for activation of c-kit through SCF and ERK phosphorylation through RAF by a flow cytometry assay.
Results: 42 pts were enrolled (4 MDS, 38 AML; median age 70, range 37-82; prior chemotherapy: 22 pts); by dose level: 100 mg bid: 7 pts; 200 mg bid: 12 pts; 400 mg bid: 17 pts. Dose limiting toxicity was observed in 0/7 pts at 100 mg, 2/12 pts at 200 mg and 1/17 pts at 400 mg; however 8/17 at the highest dose level received <14 days of treatment (7 on the 28 d arm, 1 on 14 d arm), 6 due to toxicity (abdominal pain, nausea, vomiting, rash, stroke, thrombocytopenia) and 2 because of PD, suggesting this dose is poorly tolerated in this population. Six additional AML pts were treated with 300 mg bid x 28 days, without DLT. One CR lasting 3 cycles was observed (400 mg continuous), and clinical effect (reduction in blood and bone marrow blasts) observed in 6/27 evaluable pts (1 at 100mg and 2 at 200 mg, intermittent arm; 1 each at 200 mg, 300 mg and 400 mg, continuous). Nine of 27 evaluable pts had an internal tandem duplication (ITD) of flt-3; clinical effects (including the one CR) have been observed in 3/6 pts with flt-3 ITD vs 1/10 with unmutated flt3. Biologic activity (inhibition of p-ERK in SCF stimulated PB blasts) was observed in 5/14 pts, all at 400 mg bid dose level.
Conclusions: BAY 43-9006 is an orally active C-RAF inhibitor that is tolerable at 300 mg BID in pts with AML, with early clinical and biological activity. Further study in AML with flt-3 ITD is warranted.

581PD PAX5 expression in acute leukaemias: higher B-lineage specificity than CD79a and selective association with t(8;21)-AML

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Aim: The transcription factor PAX5 plays a key role in B-lymphopoiesis, but its expression in acute leukaemias (ALs) has not been thoroughly investigated. Here we analysed routine biopsies of 360 ALs of lymphoid (ALLs) and myeloid (AMLs) origin with a specific anti-PAX5 monoclonal antibody, and compared PAX5 expression pattern with that of CD79a, the best B cell marker currently available for AL diagnosis by immunohistochemistry (IHC).
Results: In B-ALLs (n=150) blasts showed strong PAX5 nuclear staining, and co-expressed CD79a in almost all cases. However, 5 samples were PAX5+/CD79a-, due to possible CD79a antigen denaturation related to fixation/embedding procedures in 3 cases, and, importantly, to true absence of the CD79a protein in 2 cases. PAX5 labeling highlighted the nuclear irregularities of blasts, thus facilitating detection of minimal bone marrow infiltrates especially in post-chemotherapy samples. Conversely, PAX5 was detected in none of the T-ALLs (n=50) analysed, including 20 aberrrantly co-expressing CD79a.
Among 160 cytogenetically/molecularly characterized AMLs, PAX5 was selectively expressed in 15/42 cases bearing the t(8;21)/AML1-ETO rearrangement. We next extended the analysis of PAX5 expression in t(8;21)-AML at the mRNA level by means of real-time RT-PCR studies, that showed a similar up-regulation of PAX5 transcript in all eight t(8;21)-AML tested samples (including four PAX5-negative at IHC) as compared to 8 control samples lacking t(8;21). This finding suggests that PAX5 is expressed in t(8;21)-AML more widely than shown by IHC. Interestingly, PAX5$^+$ t(8;21)-AMLs co-expressed also CD79a and/or CD19 (major transcriptional targets of PAX5 in B cells) in 10/12 evaluable cases.
Conclusions: Our results indicate that: i) for ALL diagnosis, PAX5 is more B-cell specific than CD79a, and it can correctly assign to the B-lineage also cases unreactive to CD79a staining; ii) among AMLs, PAX5 expression selectively clusters with the t(8;21)/AML1-ETO rearrangement, allowing its easy recognition by IHC in a proportion of cases and likely explaining a peculiar biological feature of this subset of AMLs, i.e. the aberrant expression of B cell genes such as CD19 and CD79a.

582PD Chromosome 7 deletions are associated with unfavorable prognosis in patients with myelofibrosis

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Background: An abnormal karyotype has been correlated with poor prognosis in myelofibrosis with myeloid metaplasia (MF) in several recent studies. The feasibility and significance of conventional cytogenetics is hampered by the difficulty of obtaining sufficient numbers of analyzable metaphases from bone marrow aspirates in MF. This obstacle can be overcome by fluorescence in situ hybridization (FISH). A correlation between FISH results and prognosis has not been performed.
Methods: In this study, the bone marrow of 107 patients with MF was analyzed using FISH. The prognostic impact of individual cytogenetic lesions on survival was evaluated using multivariate analysis.
Results: Up to now, this is the largest study using FISH in MF. In univariate analysis, -7/7q- was significantly associated with inferior outcome (median survival 99 vs. 25 months, $p<0.001$). This abnormality remained significant in a multivariate analysis including all cytogenetic parameters, our own myelofibrosis prognostic index (MPI) and the LILLE prognostic score. When a cytogenetic risk indicator (CPI), based on several cytogenetic variables, was used, patients were clearly divided into two groups with a significantly distinct outcome.
Conclusion: FISH can be performed on paraffin-embedded material of patients with MF. Loss of 7/7q as determined by FISH is associated with inferior outcome in MF, even when compared to established clinical prognostic models. Chromosome 7 deletions were reported to be associated with adverse prognosis in acute myeloid leukemia and myelodysplastic syndrome. Thus our findings underline the prognostic significance of chromosome 7 deletions in myeloid disorders. By using FISH and chromosomal probes for -7/7q-, a subset of patients with MF and poor prognosis can be identified.

583P High efficacy and good tolerability with rituximab *in vivo* purging followed by autologous peripheral blood stem cell transplantation (APBST) in non-Hodgkin's lymphoma (NHL)

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High dose chemotherapy (HDCT) supported by APBST has been shown to be superior over standard therapy in a variety of settings in NHL. However,

many patients relapse due to minimal residual disease (MRD) in vivo or in the graft. Rituximab has the potential to clear both blood and bone marrow of malignant CD20$^+$ cells, prompting this multicenter trial of *in vivo* purging with rituximab and HDCT. Cyclophosphamide 4g/m^2 was used for mobilization. CY/TBI, BEAM or CBV could be used as HDCT at the discretion of the institution. Four infusions of rituximab (375 mg/m^2) were given: prior and on day 7 during mobilization, and on day -1 and +8 during transplantation. BCL-2/Ig-H as a marker of MRD was sampled from blood or bone marrow before mobilization and during transplantation using the real-time quantitative pcr technique.
Thirty-one patients from 12 centers with pathologically proven CD20+ NHL (28 aggressive, 3 indolent NHL) were enrolled. Twenty-four patients were previously untreated, and 7 patients had relapsed disease. Median dose of CD34$^+$ and MNC collection were 5.9×10^6/kg and 4.4×10^8 /kg respectively. Median time to recovery of WBC $>1.5\times10^9$/L and ANC $>0.5\times10^9$/L and platelets $>20\times10^9$/L or $>50\times10^9$/L was 10, 10, 10 and 13 days respectively. Generally the therapy was well tolerated with relatively few side effects attributable to rituximab.
All patients achieved a complete remission after APBSCT. At a median-follow-up of 12 months, overall survival (OS) and progression free survival (PFS) are 87% and 73% respectively. OS and PFS in patients with aggressive NHL are 85% and 73%, in indolent NHL 100% and 67%. In previously untreated patients OS and PFS are 88% and 73%, for relapsed patients OS and PFS are 83% and 69%, respectively. One out of the 5 patients who were initially found to be positive in the Ig-H test progressed accompanied by a rising Ig-H. On the contrary, the other 4 patients who remain in CR demonstrated a constant decline of Ig-H levels in the blood, indicating a possible predictive role of Ig-H and the efficacy of rituximab in purging MRD. These results suggest that the regimen of rituximab combined with HDCT and APBST in NHL patients is effective and safe.

584P Sequential treatment with alemtuzumab and rituximab can induce long-term responses in splenic marginal zone B-cell

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Background: Splenic marginal zone lymphoma (SMZL) is a distinctive and well-characterized B-cell neoplasm that involves the spleen and various organs. Rituximab has a significant activity in SMZL, even if cytokine release syndromes are a potentially life threatening event in patients (pts.) with a high circulating tumor load as was also experienced by us. Alemtuzumab, which binds to the CD52 antigen, can induce a good response in a substantial proportion of pts. with a mature B cell lymphoproliferative disorder, however, its use has rarely been reported in SMZL.
Methods: We here report our results in six patients (pts.) with SMZL, treated with Alemtuzumab subcutaneously (s.c.) before Rituximab as consolidation. Indication for therapy included massive splenomegaly, elevated LDH and β_2-microglobulin. The median age was 64 years (3 male, 3 female). Prior therapy included Chlorambucil (3 pts.), Fludarabine (3pts). Alemtuzumab was administered at a dose of 30 mg s.c. three times a week for 12 wks. All pts. received prophylactic Trimethoprim/Sulphamethoxazole and Valacyclovir. In four of the six pts., Alemtuzumab treatment completely resolved splenomegaly with the normalization of their blood cell count. One patient had partial response after Alemtuzumab, the sixth patient developed a transformation into a large cell lymphoma. All five pts who responded to Alemtuzumab were administered Rituximab 375mg/m^2 weekly for 4 weeks. The patient with PR after Alemtuzumab had a CR, the other pts maintained CR. No relapses have been observed to date after a median follow-up of 11 months (4-16). Two cases of CMV reactivation have been observed, only one being symptomatic and with a need of Gangiglovir.
Conclusions: Our results suggest that this therapy should be considered when splenectomy is not feasible and/or when Rituximab is not indicated as a frontline therapy.

585P Inferior complete response rates of Chinese patients with bulky mediastinal/advanced stage Hodgkin lymphoma to Stanford V regimen

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Background: The Stanford V regimen was reported to have a high remission rate in Caucasian patients with bulky mediastinal (Stage I/II) or advanced-stage (StageIII/IV) Hodgkin disease. Here we report our experience with this regimen in Chinese patients with such disease.
Patients and methods: From 1996 to 2002, nineteen patients were treated in Queen Mary hospital for bulky mediastinal/advanced stage Hodgkin's lymphoma. All patients received Stanford V regime as primary chemotherapy treatment, followed by local radiotherapy. The primary end-point was response, and the secondary end-points were disease-free survival (DFS) and overall survival (OS).
Results: With median follow-up of 33 months, nineteen patients were analyzed: twelve patients in stage I/II with bulky mediastinal disease, and seven patients with advanced stage disease. Eighteen cases were nodular-sclerosing histology, and one case was mixed cellularity. Twelve patients (63%) had B symptoms and 14 patients (74%) had high LDH on presentation. Eight patients (47%) achieved complete response (CR) while 11 patients (53%) achieved partial response (PR) with the Stanford V regimen alone. Five patients in partial remission with Stanford V chemotherapy achieved complete remission after irradiation. Six patients (32%) had refractory disease and three patients relapsed after achieving CR; of these, seven (78%) patients responded to salvage chemotherapies and/or autologous bone marrow transplant.
The projected OS was 95% at 5 years, and projected DFS was 47% at 5 years. One patient died of progressive Hodgkin disease. The commonest toxicities were gastrointestinal upset (30%) and numbness (25%). No iatrogenic mortality occurred.
Conclusion: The response to Stanford V regimen was inferior in Chinese patients when compared with historical Caucasian counterparts, with poorer CR rates (47% vs 72) and lower DFS (47% vs 89%). However, most patients with refractory/relapsed disease responded well to salvage chemotherapies followed by bone marrow transplant, accounting for similar progression rates (95% vs.96%).

586P BEACOPP (basic & modified escalated) chemotherapy for Hodgkin's disease (HD): A cost effective protocol in developing country

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Introduction: In HD, ABVD has been challenged with newer regimens e.g. BEACOPP & Stanford V. BEACOPP shows significant benefit in reduction of early failure to CT.
Objective: To achieve higher response rate with shorter duration & cheaper regimen in developing countries.
Material & Method: 20 previously untreated pts. from April 2000 to Jan 2003. Risk factors used were $\geq$3 L/node areas, high ESR, extra nodal involvment or bulky mediastinal mass. Stage I & II without risk factor were classified as "early stage" group. Stage III/IV & stage I & II with any risk factor were classified as "advance stage". 4-6 cycles of basic BEACOPP were given in early stage. In advanced stage 6 cycles of "modified Escalated BEACOPP" (with increasing dose of Adriamycin to 30 mg/m^2 and Bleomycin 10 mg/m^2 on D1 & 8 were given. Involved filed RT 30Gy, in all early stage & 40Gy in advance stage with bulky/residual was given.
Results: Early stage/advance stage pts were 5/15. 19 pts completed planned CT. All early stage pts. achieved complete response. In advance stage 13/15 (86%) responded to CT. Toxicity Grade III or IV anemia, neutropenia, thrombocytopenia were 10/105 (9.4%), 10/105 (9.4%), 6/105 (5.71%) respectively. Total cost of ABVD chemotherapeutics drugs is US $ ~900 while basic BEACOPP is of ~450 and modified Escalated BEACOPP is ~550. Similarly one and half month treatment duration is also reduces.
Conclusion: Basic and modified Escalated BEACOPP are equally effective in short-term results with reduced cost & duration. Long term & randomized data are required before it replaces ABVD.

587P Liposomal doxorubicin in combination with vincristine, cyclophosphamide and prednisone in patients with aggressive diffuse large B-cell lymphomas (DLBCL)

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CHOP is standard therapy for patients (pts) with aggressive DLBCL. However its clinical use is limited by several general toxicities: particularly cardiotoxicity, peripheral neuropathy, mycoses, myelosupression etc. dose-limiting toxicities, restricting cumulative dose.
Liposomal formulation of drugs that allows for delayed clearance by the reticuloendothelial system, prolonged circulation time, retention drug in the

liposome while in circulation, and concentration of drugs in tumors with high vascular permeability.
Methods: Twenty-four pts with DLBCL, aged 54 to 77 years median age was 65 years, without previous treatment, high and high-intermediate IPI (11 pts), stage III - IV (14 pts) were treated with the CHOP regiment at standard dose with liposomal doxorubicin (LD) - L - CHOP. Dose level of vincristine - 2 mg IV, liposomal doxorubicin - 60 mg/m^2, cyclophosphomide 750 mg/m^2, prednisone 60 mg/m^2 p.o. 5 days, administered every 3 weeks. The median number of prior regimens was 3 (range 2 - 6).
Results: The best response was a complete response in 20 pts (83%), partial response in 3 pts (12%). At a median follow-up of 18 months relapse has been in 1 pts (5%) after 3 month for respondents. Toxicity was mild: 2 pts had grade 1 neutropenia, 3 pts had grade 1-2 anemia, cardiac toxicity - 1 pts (after 4 courses) other pts cardiac function was normal during and 18 month after chemotherapy. Rens and hepatic function saved normal too. Peripheral neuropathy has not been observed.
Conclusion: liposomal doxorubicin vincristine are effective and well tolerated in treatment for patients with aggressive non - Hodgkin's lymphoma. Regime L-CHOP appears to be an acceptable alternative for elderly patients.

588P CHOP chemotherapy (ct) with rituximab and radiotherapy (RT) as a first line treatment for aggressive non-Hodqkin's lymphoma (NHL) - our experience

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Background: In advanced aggressive NHL CT is a basic treatment. Additional involved-field RT may achieve a better outcome.
Aims: In this study we combined two modalities of treatment (CHOP regimen with the monoclonal antibody rituximab and RT) and assessed their role.
Material and Methods: We treated 40 patients (pts) with advanced aggressive NHL initially with the CHOP regimen plus rituximab. There were 26 male and 14 female, median age was 53 years (range 43-68), with stage III or IV disease. RT was given to 16 (40%) of pts. Indication for RT included initial bulky disease and lack of complete remission (CR) after CT. involved-field RT was used with one fraction per day of 1.8 Gy, to a total dose delivered by 19-22 fractions. Response was assessed at two months after the end of RT and then every three months. The primary end point was freedom from progression (FFP) and overall survival (OS) after 3 years. Median observation time was 26 months.
Results: The rate of complete remission (CR) was 60% after CT.
Following RT the rates of CR and PR were 81% and 19%, respectively. Three-year FFP and OS in pts who received RT were 71% and 79%, respectively. In pts who were treated with CHOP+rituximab alone 3-year FFP and OS were 52% and 61.5%, respectively. Univariant analysis showed that stage, extranodal involvement, performance status, LDH level, are significant prognostic factors for survival.
Conclusion: Combination of these two modalities CT and RT showed better outcome as a first-line treatment for pts with advances aggressive NHL, than applied CT alone.

589P Phase II open study using Rituximab (MabThera) + CHOP in treatment of pts with diffuse large B-cell Lymphoma (DLCL)

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Introduction: Rituximab (MabThera) is the first monoclonal antibody approved for the treatment of pts with relapsed or refractory CD20+ low grade non-Hodgkin's lymphoma (NHL). The mechanism of action of Rituximab is a mixed one, mainly by complement dependent cytotoxicity, antibody dependent cellular toxicity, induction of apoptosis and working as a chemosensitizer in pts who develop multiple drug resistance during treamtent.
DLCL is the most common type of aggressive lymphoma and considered for about 40% of all NHL cases. Use of different chemotherapy regimens didn't change the response or survival of pts in comparison with CHOP. Studies by Coiffer showed some progression in treatment of elderly pts with aggressive NHL adding Rituximab to std CHOP chemotherapy. In this study we tried to show MabThera+CHOP is an effective regimen and it works in young pts as well as elderly ones.
Material & Method: To study the efficacy of Rituximab added to std CHOP in pts with DLCL, 20 pts were treated with the following regimen:
All pts were scheduled to receive 6-8 cycles of treatment.

Rituximab (MabThera)	IV 375 mg/m^2	Day 1	q 3 weeks
Cyclophosphamide	IV 750 mg/m^2	Day 1	q 3 weeks
Doxorubicin	IV 50 mg/m^2	Day 1	q 3 weeks
Vincristin	IV 2 mg/m^2	Day 1	q 3 weeks
Prednisone	IV 100 mg po	Day 1-5	q 3 weeks

All pts had high grade DLCL, Stage IV (except one pt with stage I). PS varies between 1-3.
Results: 9 pts received full treatment and the rest of the pts had 3-5 cycles of chemotherapy. 19 out of 20 pts achieved complete remission almost at the 2nd cycles. We did not observe any additional toxicity due to Rituximab+CHOP in comparison with the known toxicities of CHOP. These data show that the combination of Rituximab with std CHOP will cause rapid response and is effective in both young and elderly pts with DLCL.
Conclusion: Rituximab+CHOP is highly effective in induction of response in pts with DLCL. It is as effective in young pts as elderly ones. Especially it is highly effective in pts with advanced destructive primary bone lymphoma as all of cases are in CR up to 24 months with full activity. Study needs more pts and time to evaluate the duration of response and OS in pts treated with this combination.

590P Thalidomide-dexamethasone combination in symptomatic multiple myeloma: An Indian experience

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Background & purpose: Thalidomide is a well-established anti-angiogenic agent used extensively in relapsed multiple myeloma. We evaluated the activity of thalidomide-dexamethasone combination in patients of symptomatic myeloma.
Patients and methods: Thirty seven patients (23 untreated, 14 pretreated) were treated with thalidomide (THALIX® 200mg) orally at bedtime and received dexamethasone 40mg for 4 days beginning on days 1, 9, and 17; the second and third cycles of repeated dexamethasone were begun on day 30. Both group of patients were treated for at least 4 months. Response was assessed on the basis of reduction in paraprotein levels in the serum and reduction of myeloma cells in the bone marrow.
Results: 20/23 newly diagnosed patients (87%) and 8/14 (57.1%) pretreated patients showed an objective response as per SWOG criteria. 16/23 (69.6%) untreated myeloma patients and 3/14 (21.4%) pretreated myeloma patients showed a complete response. The median time for achieving the best response was 8.2 weeks. 2/23 (8.7%) & 3/14 (21.4%) patients had stable disease in the untreated & pretreated groups respectively. Only 4/37 (10.8%) patients had a documented disease progression. Most commonly observed toxicities include peripheral neuropathy (51.4%), constipation (51.4%), sedation (37.83%) and rashes (24.32%). Only in one patient Grade 3 peripheral neuropathy and rashes were noticed. No Grade 4 toxicity was observed during the study.
Conclusion: The combination of thalidomide with dexamethasone indused a high frequency of response and low incidence of serious irreversible toxicity. These observations support further studies of this promising combination for patients with newly diagnosed multiple myeloma.

591P Lomustine, Ifosfamide, Bleomycin, Vincristine, and Cisplatin (CIBO-P) is an effective regimen for patients (pts) with poor prognostic refractory or multiply relapsed aggressive non-Hodgkin's lymphoma

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Background: Despite advances in the management of aggressive non-Hodgkin's lymphoma, the treatment of multiply relapsed and refractory disease remains a major challenge. Cisplatin-based combinations have proven to be an effective choice for patients with relapsing or refractory lymphoma, particularly for pts with favorable prognostic characteristics.
Patients and methods: 43 consecutive pts with relapsed or refractory non-Hodgkin's Lymphoma were treated with Lomustine (60 mg/m^2 d 1 or 2), Ifosfamide (1.5 g/m^2 d 1, 2 and 21, 22), Bleomycin (5 mg/m^2 d 1, 5 and 21, 25), Vincristine (1.4 mg/m^2 d 1, 8 and 21, 28) and Cisplatin (25 mg/m^2 d 3, 4, 5 and 23, 24, 25) given every 42 d [CIBO-P regimen].
Results: 39 patients (91%) were evaluable for response. The median age was 60 years (range 26-83). Histological subtypes were: diffuse large B cell (n=32), extranodal diffuse large B cell (n = 4), anaplastic large cell (n=2) and T-lymphoblastic lymphoma (n=1). 40% of the pts had previously

been treated with more than 1 line of prior chemotherapy and 53% had elevated lactate dehydrogenase levels at the time of treatment initiation. The median remission duration prior to receiving CIBO-P was 195 d. The overall objective response rate was 76% [95% Confidence Interval (CI): 58-90%], including 21 (52%) complete and 9 (24%) partial responses. CIBO-P induced responses in all histological subtypes, primary refractory disease and pts treated at second or subsequent relapses. The median duration of response was 7.5 months (95% CI: 1.1-17 months) and the median survival duration was 12 months (95% CI: 5.9-18.1 months). Myelosuppression was the most frequent serious complication of this regimen. However, no cases of hemorrhage with thrombocytopenia, and only 6 (14%) cases of febrile neutropenia were encountered.
Conclusions: CIBO-P is a novel combination salvage therapy for poor-prognostic refractory or multiply relapsed aggressive non-Hodgkin's lymphoma pts. It has clinically significant activity with a favourable toxicity profile.

592P Continuous Erythropoiesis Receptor Activator (CERA) provides dose-dependent erythropoietic activity with a prolonged half-life in healthy volunteers

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Treatment of anemia is an integral part of cancer management. There is a clinical need for effective medications that can be administered at less frequent dosing intervals, offering flexibility and convenience to patients and medical staff. Preclinical studies indicate that Continuous Erythropoiesis Receptor Activator (CERA) is an innovative erythropoiesis-stimulating agent with a prolonged half-life, acting differently at the receptor level. This evidence suggests that CERA may provide effective stimulation of erythropoiesis when administered at less frequent dosing intervals. The objective of these Phase I studies was to evaluate the pharmacodynamics (PD) and pharmacokinetics (PK) of CERA when administered in multiple ascending doses. Healthy volunteers (N=116) were enrolled in 2 open-label, parallel group, placebo-controlled studies. Subjects were randomized to receive: CERA (0.4, 0.8, 1.6 or 3.2 μg/kg) either by intravenous (IV) injection once every 3 weeks (study days 1, 22 and 43; n=61) for a total of 3 injections; or by subcutaneous (SC) injection once every 2 weeks (study days 1, 15, 29 and 43; n=48) for a total of 4 injections; or placebo. CERA induced a rapid, dose-dependent, erythropoietic response; increases in reticulocyte count peaked at 7 and 10 days after IV and SC administration, respectively. The PK of CERA did not appear clinically affected by repeated dosing. Serum half-life of CERA ranged from 70-140 h for IV administration and 73-170 h for SC administration. CERA was generally well tolerated; no serious adverse events were attributed to study agent. Antibodies were not detected in any subject. In healthy volunteers, CERA administered by IV or SC injection was well tolerated and demonstrated prolonged, dose-dependent erythropoietic activity. Serum half-life was considerably longer than that of currently available erythropoietic agents.
These data suggest that CERA can be administered with extended dosing intervals, which may enable administration on the same dosing schedule as some chemotherapy agents, offering flexibility and convenience in managing cancer-related anemia. Phase II trials in patients with cancer are ongoing.

593P Continuous Erythropoiesis Receptor Activator (CERA) produces dose-related erythropoietic activity in patients with multiple myeloma

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Continuous Erythropoiesis Receptor Activator (CERA) is an innovative, erythropoiesis-stimulating agent with a prolonged half-life acting differently at the receptor level. This exploratory, multicenter, open-label study of adults with multiple myeloma (MM) receiving chemotherapy and with anemia (hemoglobin [Hb] ≤11 g/dL) aimed to identify a suitable CERA dose range for further clinical testing. Patients (n=64, randomized groups of 8-10) received CERA subcutaneously (SC) (2.0, 3.5 or 5.0 μg/kg) once every 3 wk for 6 wk (core period), optionally extended to 12 wk. After reviewing efficacy and safety data, extra patients were assigned sequentially to doses of 6.5 and 1.0 μg/kg, then 8.0 and 4.2 μg/kg. Demographics were similar in all patient subgroups. CERA produced a rapid, clinically relevant, dose-related increase in Hb (regression analysis of the change from baseline to end of initial treatment [core study period completion, transfusion or dose change]). Mean Hb increased 1.6-2.3 g/dL with CERA 3.5-8.0 μg/kg and 50%-62.5% of patients had a response of ≥2 g/dL during the core period. Levels were maintained or improved from 6-12 wks. A plateau in response was seen at 5.0-8.0 μg/kg. CERA was generally well tolerated. AEs attributed to CERA were rare (5 hypertension, 1 pyrexia, 1 allergic dermatitis) during the core period. There were no unexpected clinical and laboratory measurements, and no evidence of antibody development. In patients with MM, CERA administered SC once every 3 wk produced a rapid and sustained increase in Hb.
The long dosing interval of CERA may enable administration on the same dosing schedule as some chemotherapy agents, offering flexibility and convenience in treating cancer-related anemia.

594P Phase II study of prolonged administration of arsenic trioxide (ATO) in patients with Myelodysplastic Syndromes (MDS) and Chronic myelomonocytic leukemia(CMML): M D Anderson Cancer Center experience

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We examined the value of prolonged administration of ATO (Trisenox®) in patients (pts) with MDS and CMML.
Treatment: ATO (0.25 mg/kg/day) was given 1 hr i.v. infusion daily × 5 days followed by 0.25 mg/kg twice weekly for 11 weeks. Pts were assessed at 4 weeks, after the first course, then monthly. Pts. with stable disease were eligible for further courses.
Patients: 17 patients enrolled: 14 RBC transfusion-dependent MDS (6 RA/RARS, 8 RAEB; 12 IPSS risk Low/Int1, 2 Int2/High), and 3 CMML. Median age was 67 years (y) (range 46-84). 6 had history of previous treatment other than supportive care. 16 were evaluable for toxicity and response. 1 received 3 courses, 3 received 2 courses, and 13 received 1 course.
Results: Hematologic responses (IWG criteria) were observed in 4 patients (25%).

Type of response	Time to response	Duration
Minor erythroid	2 mo	3+ mo, RBC transfusion-dependent
Major neutrophil and platelet	2 mo	7 mo
BM blast decrease 15% to <5%	1 mo	7+ mo, stable cytogenetics
Hematologic/cytogenetic CR*	1 mo	9 mo

*Most significant response. 76 y old male, RAEB-2, Int 2, complex chromosomal abnormalities, previously failing thalidomide for 6 mo and thalidomide + cyclosporin A for 3 mos.
Of 3 CMML, one pt. had transient reduction of absolute monocyte counts during each of 2 courses; all 3 CMML had stable disease.
Toxicities: In 24 courses there were 6 febrile episodes requiring admission, all in pts. with pre-existing neutropenia; 1 Gr 3 and 1 Gr 4 thrombocytopenia, 1 Gr 3 neutropenia, all requiring dose modification; 1 episode accelerated functional cardiac rhythm; and 1 anemia-precipitated congestive heart failure unlikely related to the drug. There were 22 episodes of Gr 1 or 2 drug-related toxicities.
Conclusions: 4 responses of 3-7+ mo. duration were observed, including 1 CR, suggesting activity in as yet undefined subgroup of MDS. No benefit of prolonged treatment was documented. ATO was safe in outpatient setting for elderly patients. Observed low toxicity and documented activity suggest potential use of ATO for combination therapy of MDS.

595P Collection of autologous peripheral blood stem cell in 71 patients with relapsed or refractory hodgkin's lymphoma using ESHAP + G-CSF 300 microgram sc twice a day

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Objective: To review our experience with ESHAP chemotherapy as autologous peripheral blood stem cell (PBSC) mobilization regimen in patients with hodgkin's lymphoma (HD) undergoing PBSC transplant (PBSCT).
Methods: Patients with relapsed or refractory HD who received ESHAP (continuous infusion of cisplatin) from 1996 to May 2004 as salvage chemotherapy prior to PBSCT were reviewed. Responding or stable HD

patients received ESHAP for mobilization of PBSC. These patients received fixed dose G-CSF 300 mcg SC twice a day starting 24 hours after finishing mobilizing ESHAP. Daily apheresis using COBE Spectra BCT, to collect a minimum of 2 x10*6 CD 34+ cells/kg body weight was initiated when peripheral blood CD 34 + cell count exceeded 20 CD 34+ cells/microliter. Apheresis volume guideline was 10 liter (< 70 kg patients), 12 liter (70-95 kg), and 15 liters (> 95 kg). patients < 60 kg often had < 9 liters due to tolerability. Product volume, CFUC-GM, CFUC-GMME, and CFUC-E (BFUE) were recorded.
Results: Characteristics of 71 patients with adequate CD 34 + collection are: 37 males: 34 females. Initial stage I:II:III:IV: unknown was 4: 20: 21: 24: 2 respectively. Median age at initial diagnosis was 19 yrs (9 to 60 yrs). Median number of cycles prior to ESHAP was 7; 80% had < 8 cycles and 20% > 8 cycles. Median ESHAP cycle used as mobilizer was 3 (1st or 2nd in 10 patients, 3rd in 51 patients, 4th in 10 patients. 73% patients required only 1 apheresis and 27% had > 1 apheresis. Median total and per kg. CD34+ cells collected were 475×10^6 and 8.77×10^6/kg respectively. Cells collected for patients weighing <70 kg (55 patients) were 8.9×10^6/kg and for patients >70 kg (16 patients) was 9.05×10^6/kg. For 52 patients who required only one apheresis, CD 34 + cell yield was 10.25×10^6/kg and for those who required >1 apheresis (19 patients) it was 5.5×10^6/kg.
Conclusion: ESHAP and fixed dose G-CSF is an effective mobilizing regimen. Most patients require only 1 apheresis. Fixed dose G-CSF at 300 microgram sc twice a day is adequate in producing desired CD 34 + cells for apheresis even in patients > 70 kg.

596P Successful treatment of Lymphoid granulomatosis with anti-CD20 monoclonal antibody rituximab - rationale and a case report

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Rationale: Lymphoid granulomatosis is a rare angiocentric and angiodestuctive Epstein-Barr virus-positive B-cell lymphoproliferative disorder. Treatment options include corticosteroids, antiviral therapy with interferon alpha and ganciclovir as well as combination chemotherapy however long term prognosis is very poor. Current available data suggest a beneficial role of Rituximab even in the treatment of aggressive CD 20+ B-cell non-Hodgkins lymphoma.
Case report: A 21-year-old white woman was admitted for evaluation of a mediastinal bulk (50 x 60 mm) diagnosed in May 2002. Except chronic cough her health status was not impaired. Thoracotomy and biopsy specimen was revealed after uncertainty of the diagnosis: CD 20+-lymphomatoid granulomatosis with clear EBV-association. Bone marrow biopsy specimen were normal. Computed tomographic scans showed no hiliar and abdominal lymphadenopathy.
In regard of the EBV associaton and lack of standard therapy options, we initiated an antiviral therapy with Valganciclovir. After 2 months of continuing treatment and no change of the mediastinal bulk, treatment was completed with interferon-alpha. After responding to that combination therapy shortly with a moderate decrease of the tumour, MR-imaging of the thorax in October 2002 showed progresion of the mediastinal bulk On the basis of positive expression of CD 20 on the lymphoid cells we started treatment with Rituximab with four weekly doses of 375 mg/m^2 followed by a monthly schedule until August 2003. After 3 months of treatment MR-imaging of the thorax showed an remission of the bulk from 80 x 60mm to a residual tumor mass with a size of 10 × 15 mm. From August 2003 to May 2004 the pt did not receive any specific therapy and the pt remains relapse free until now. During the whole treatment period the pt did not experience any therapy-associated side effects and was able to work in a full time job as a nurse. For consolidation radiotherapy of the initial bulk was performed.
Conclusion: Rituximab is a well tolerated treatment option with a favourable toxicity profile even in rare aggressive CD20+ lymphoproliferative disorders like Lymphoid granulomatosis which can induce striking remission as shown.

597P Primary lymphoma of bone: a retrospective study

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Objective: This retrospective study describes our experience with the diagnosis, treatment, results and long-term follow-up of primary bone lymphoma (PBL).
Patients and Methods: Nineteen patients diagnosed with PBL were reviewed: 7 with stage I_E disease, 4 with stage II_E (regional lymphadenopathy), 8 with stage IV disease (disseminated bone involvement). Only one stage IV patient exhibited "B" symptoms. The majority (72%) demonstrated diffuse, large cell, B-type lymphoma. All patients were treated with adriamycin-based chemotherapy and consolidation radiotherapy to the primary site (8 patients: early PBL) or the most bulky area (3 patients: stage IV PBL) (median total dose: 3,988 cGy; range: 3,960-4,000 cGy).
Results: Ten stage I_E/II_E patients are alive with no evidence of disease (NED). One died due to metastatic secondary lung cancer while with NED from his PBL. Eight stage IV patients are alive with NED. Median follow-up for all living patients: 77 months. Side effects were mild and did not necessitate delay in treatment.
Conclusions: Our departmental policy of treating PBL patients with an anthracycline-based regimen and involved field radiotherapy proved to be successful in achieving excellent long-term, disease-free survival. Phase III randomized, controlled, clinical trials will determine the true role of consolidation radiotherapy in PBL, when considering severe late side effects, including radiation-induced bone tumors.

598P Second primary tumors in mycosis fungoides patients

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Background: Mycosis Fungoides [MF] patients enjoy long-standing remissions following total skin electron irradiation [TSEI] but run the risk of developing secondary malignancies.
Patients and Methods: From 1979 to 2002, 84 patients with biopsy-proven MF were referred to our department for TSEI, until 1992 using the modified Christie Hospital translational technique and since 1992 the Stanford technique. Median total dose was 32 Gy (range, 16-44 Gy) Christie; 30 Gy (range, 15-36 Gy) Stanford. Underdosed areas were boosted with a median total dose of 100-200 Gy.
Results and Conclusions: During a median follow-up of 73 months (range, 2-191 months) from the end of TSEI, 13 (15%) patients developed 20 second primary tumors within the irradiated areas - lymphoma: 2; skin cancer: 7; melanoma: 2; solid tumor: 9. Six patients developed second primaries either simultaneously with the newly diagnosed MF or prior to introduction of radiation therapy. The long-term prognosis was related solely to the second primary. Due to excellent long-lasting response rates following TSEI coupled with long-term survival, and the prognosis mainly associated with the stage and histology of the second malignancy, physicians should be aware of the possibility of second primary tumors.

599P Primary extra nodal lymphomas: analyses of clinical characteristicsa single centre experience

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Background: Primary extra nodal Non-Hodgkin's lymphoma has varied presentations. Emphasised in this study are the clinicopatholgical characteristics and outcome of extra nodal Non Hodgkin's Lymphomas according to the primary sites of the disease.
Patients and methods: A retrospective analysis of 615 patients treated for Non-Hodgkin's lymphoma between January 1989 to December 2003 was done. 150 patients (24.39%) were categorised as extra nodal lymphoma. The cases diagnosed prior to 1994, were converted into WHO classification. The characteristics of patients were as follows: Median age 46 years (15-86) with 95 males (63.33%) and 55 females (36.66%). Pathological subtypes were follicular and other low grade variants in 27, diffuse large and other high grade subtypes in 112, MALT variety in 11 patients. IPI among the high-grade histology were low risk - 71, low intermediate - 17, high intermediate - 10, high - 6, and data missing in 8 patients. 60 patients (40%) presented with primary extra nodal, 64 (42.66%) with regional lymph node involvement and 26(17.33%) with extensive involvement. Patients were treated with all three modalities chemotherapy, surgery, and radiotherapy either alone or in various combinations. Six patients did not receive any treatment.
Results: Distribution of extra nodal sites according to the primary site was gastrointestinal tract (n=58) musculoskeletal (n=16), tonsil (n=15), mediastinal (n=14), oral cavity and sinuses (n=11), liver & spleen (n=6 each), CNS (n=5), thyroid (n=4), testis, kidney, lung, tongue, salivary gland (n=2 each), skin, pleura, ovary, vagina, pancreas (n=1 case each). After a median follow-up of 25 months (0-179), overall survival was 88% and disease free survival was 78%. Eighteen patients died, out of which 14 due to disease recurrence or progression.

Conclusion: Achieving a complete remission shows a favourable prognostic index for survival. Poor prognostic factor identified was high grade histology. Age, IPI index and disseminated disease did not affect the survival in our study thereby differing from nodal NHL. Incidence, distribution and outcome (Overall survival and DFS) were comparable to other studies; however the median follow in this analysis was short.

600P Lympho-reticular malignancies in HIV-1infected patients: Indian experience

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The incidence of lymphoma in the patients with HIV infection is rising. The outcome of these patients is considered to be poor. With use of Highly Active Antiretroviral Therapy (HAART), effective chemotherapy and improved supportive care the outcome has improved.
We present our experience of 11 patients with HIV-Lymphoma. All underwent standard staging with history, physical examination, a chest X-ray or CT thorax, CT abdomen/pelvis, complete blood count, biochemistry, bone marrow and other required tests. CD 4 count was evaluated at baseline and then every three months. Eight patients have received HAART and 3 did not fulfill criteria to start HAART. The chemotherapy schedule was CHOP for large cell lymphoma, ABVD for Hodgkin's disease (HD) and Murphy's protocol for small non-cleaved lymphoma (SNCL). The dose of doxorubicin was halved in the first cycle and escalated subsequently as per the tolerance. Response was evaluated after every 2 cycles and toxicities at every cycle.
Seven patients had large cell lymphoma, two had HD, and one each had SNCL and acute lymphoblastic leukemia (ALL). The patients had a fair tolerance to chemotherapy. All had severe neutropenia and other non-hematologic toxicities in initial cycles of chemotherapy. The tolerance improved with subsequent cycles. Of the 7 patients with large cell lymphoma, 3 are in CR from 18 to 33 months. One completed treatment at other center, was in CR but then there is no follow up, one patient died at 48 months of opportunistic infection, one died early without response and one patient declined treatment and is lost from the follow up. Of the 2 patients with HD, one is in continuous CR at 33 months and other has completed 4 cycles of ABVD and is in CR. The SNCL patient achieved a CR but is lost from follow up after completing treatment. The one with ALL died in 5 days after diagnosis of tumor lysis.
We have seen encouraging result and tolerance to chemotherapy in lymphomas in HIV infected patients. The patients need greater supportive care for neutropenia and mucositis. Our patients also required social and economical help to complete the treatment and to continue the follow up.

601P The investigation of platinum drugs reactivity in patients with CLL in vitro

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The aim of this study was to investigate the molecular mechanism(s) of apoptosis induction by new Russian antitumor platinum drug - cycloplatam in patients with chronic lymphocytic leukemia (CLL) and to compare the chemosensitivity of tumor cells derived from refractory patients with CLL to known platinum-containing drugs.
Methods: The leukemic cells were isolated by Ficoll density gradient centrifugation. The cells were incubated with 4 platinum drugs (10^{-4}M) for 4 days. Leukemic cells survival (LCS) was calculated by OD treated well/OD control wellsX100(%). LD50 was calculated from the dose- response curve. The cells were stained with PI and DNA fragmentation was determined by flow cytometry.
Results: We have tested the sensitivity of leukemic cells derived from 20 patients with CLL to different platinum-containing drugs by MTT assay. 57% of patients were sensitive to cycloplatam, 33% of patients were sensitive to oxcaliplatin, 11% of patients were sensitive to cisplatin, 14% of patients were sensitive to carboplatin. The data obtained indicate that the Russian platinum-containing drug was more cytotoxic than the other platinum drugs we used. The DNA fragmentations of leukemic cells induced by platinum drugs were studied for 14 patients. The fluorescence of propidium iodide staining cells was positive for 50% of patients when we used cycloplatam. Cisplatin and carboplatin were less effective as an apoptosis inducers: 10% and 25% respectively.
Conclusion: Platinum drugs continue to be the mainstay of curative therapy for a wide range of adult malignancies. Here, we have shown that the Russian platinum drug - cycloplatam in compare with cisplatin, carboplatin and oxaliplatin is more effective as the cytotoxic agent and as the inducer of apoptosis in leukemic cells*in vitro.*

602P Apoptotic synergism between histone deacetylase (HDAC) inhibitor and imatinib mesylate (STI571, Glivec®) on chronic myelogenous leukemia (CML) cell lines

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Even though, imatinib mesylate(STI571, Glivec®) is highly effective against Bcr/Abl positive malignancies, resistance against STI571 is on the increase. To improve the treatment outcome in CML patients, new histone deacetylase inhibitor (SK-7068) was examined. SK-7068 induced apoptosis in CML cell lines. To investigate whether combined treatment with STI571 shows synergism in CML cell lines (K562, KCL 22, BV173), assays for caspase 3 activity, FACS analysis, and western blot analysis were done. Combined treatment with SK-7068 and STI571 were more effective than either SK-7068 or Glivec alone. SK-7068 induced apoptosis in a dose dependent manner when administrated with a fixed concentration (320nM) of STI571. Combined with STI571, SK-7068 (4uM) potently induced cell death, triggering apoptosis in more than 60% of cells in 48h by FACS analysis. SK-7068 decreased cyclin D1 expression, but STI571 had no effect on the expression level of cyclin D1. CDK4 expression level was not affected by combined treatment. When K562 was treated with various concentrations of SK-7068, the level of p21 expression was gradually increased, whereas STI571 had no effect. These findings suggest that two drugs induced apoptosis via different pathways.

603P Positron Emission Tomography (PET) with fluorine-18 fluoreoxyglucose ([^{18}F]FDG) as a good tool for evaluation of response or residual disease in primary lymphoma of bone

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Primary lymphoma of bone (PLB) is one of the rarest primary bone malignancies. The main treatment modality is chemotherapy, which is different from that for other malignant bone tumors. According to the response to primary treatment, subsequent second-line treatment could be different; therefore proper evaluation for treatment effectiveness is needed. However, treatment evaluation is more difficult for bone lesion characteristics than for other lymphomas. After chemotherapy, evaluation for the viability of a residual tumor is very difficult. Viable tumors cannot be differentiated from bone fibrosis and remodeling lesions without surgical resection. Therefore, it is not easy to determine complete response accurately, and it is difficult to establish subsequent treatment strategies. We investigate the usefulness of the PET scanning in evaluation of PLB, as compared with CT and MRI scanning. A survey of 1,422 NHL patients who had been diagnosed at Korea Cancer Center Hospital between 1989 and 2003 identified 28 patients with PLB (2.0%). Among these cases, FDG-PET had been used for evaluation of diagnosis, response and recurrence in 10 cases. We analyzed and compared conventional CT/MRI findings with FDG-PET scanning findings of these cases. All these 10 cases were reviewed and confirmed by experienced hematopathologist with bone biopsy. The clinical data and imaging findings of these patients were monitored during treatment and follow-up period for change of the imaging findings. To decide the CR, PET scanning following treatment showed no hypermetabolic lesion with a rapid decline of FDG uptake. However, follow-up CT or MRI showed persistent bone lesion after Partial Response (PR). To decide the early relapse, PET scanning showed definite hypermetabolic lesions with a rapid increase of FDG uptake. However, follow-up CT or MRI showed no specific changes. Our results suggested that PET scanning was more sensitive in evaluation for response and relapse of PLB.

604P Prognostic criteria in primary non-Hodgkin's lymphomas of the spleen

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Objective: The aim of this multicentric study was to outline the prognostic criteria for primary splenic non-Hodgkin's lymphomas (PS NHL), which could be used in working out the optimal treatment strategies.
Materials and Methods: 155 patients with PS NHL were comprized by the current study. Low-grade (LG) NHL were diagnosed in 110 (70.9%) cases, and high-grade (HG) NHL - in 45 (29.1%). Of patients with LG NHL, 107 (97.3%) had the stage IV disease. Bone marrow involvement (BMI) and leukemic phase (LPh) were detected in 106 (96.4%) and 93 (84.5%) cases, respectively. Of patients with HG NHL, 38 (84.6%) had the stage IV disease, and 7 (15.4%) - the localized stage disease. The BMI and the LPh were registered in 20 (52.6%) and 6 (30.0%) patients, correspondingly.
Results: The overall 5-year survival (SV) was 55.1% in patients with LG NHL, and 28.9% - in those with HG NHL ($P < 0.05$). In HG NHL, the 5-year SV was 71.4% in cases with the localized stage disease, and 18.2% - in cases with the stage IV disease ($P < 0.05$). In LG NHL, the 5-year SV amounted to 57.8% in patients under 50 years, and 45.5% in those of 50 years and older ($P < 0.05$). In HG NHL this parameter was 28.5% and 9.8%, respectively ($P < 0.05$). In HG NHL, the 5-year SV made up 32.5% in cases without the BMI, and 24.1% with that one. In LG NHL with the BMI, the 5-year SV constituted 70.0% in patients without the LPh, and 53.0% in patients with the LPh ($P < 0.05$). In HG NHL with the BMI, the median longevity was 23.5 and 4.7 months, correspondingly ($P < 0.01$). In splenectomized patients, the 5-year SV made up 69.5% in cases with LG histology, and 47.2% - in those with HG histology. In patients treated by therapeutic modalities only, the 5-year SV amounted to 43.1% and 10.8%, respectively ($P < 0.05$). In the available cases with postsplenectomy correction of cytopenias, the 5-year SV constituted 75.0%. Patients without postoperative abolition of cytopenic syndrome failed to achieve the 3-year SV.
Conclusions: In PS NHL, the histologic type and the clinical stage of the tumour, the patient's age, the BMI, the presence of LPh, the usage of splenectomy and the postoperative correction of cytopenias are of great prognostic importance and require careful consideration regarding the expedience of treatment intensification.

605P The risk of development of disglobulinemia among breast cancer patients

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Using the data accummulated in *Centre René Huguenin* at Saint - Cloud, France, a cohort study was conducted on the occurrence of dysglobulinemia following breast cancer in females.
Of the 25165 breast cancer patients newly diagnosed in the period from 1976 till 2000, 27 developed dysglobulinemia.
The age at the time of diagnosis, histological nature, TNM classification, hormonal status and treatment received were studied. The average age at time of breast cancer diagnosis was 61.1 years. Of the 27 patients 3 were T0, 5 were T1, 11 were T2, 5 were T3, 2 T4 and 1 was unknown. 12 were node positive, 14 were node negative histologically and 1 was unknown. Only three patients were metastatic by the time of diagnosis. 2 were ER -ve, 3 were PR -ve, 10 were ER +ve, 9 were PR +ve and determination of hormonal status was not performed for 15 patients. Histologically, 18 patients had infiltrating duct carcinoma (IDC), 3 had infiltrating lobular carcinoma (ILC) and 5 had other pathologies. 23 patients underwent surgery, 15 received radiotherapy, only 4 received chemotherapy. 10 patients received adjuvant hormonal therapy all by tamoxifen.
The age at the time of diagnosis, type of immunoglobulin, stage, treatment received, the delay between breast cancer diagnosis and the discovery of dysglobulinemia were also studied for every case. In 8 of these patients dysglobulinemia was discovered at the same time as breast cancer diagnosis. The average delay between breast cancer diagnosis and the discovery of dysglobulinemia was 8.5 years. Of the 27 patients, there were 13 cases of MGUS; of these there were 6 IgG kappa, 3 IgG lambda, 3 IgA kappa, one IgM kappa. There were 6 cases of Waldenstrom; 3 IgM kappa, 2 IgM lambda, 1 mixed with IgM kappa & IgG kappa. And there were 8 cases of plasma cell myeloma, 2 IgA lambda, 2 IgA kappa, 2 IgG kappa, 1 IgG lambda, 1 light chain plasma cell myeloma.
Conclusion: The risk of plasma cell myeloma among breast cancer patients was 31 per 100,000 whereas the expected risk in normal population is 3 per 100,000. (relative risk (RR) was 10,2), which was statistically signifiant. No common risk factors for development of dysglobulinemia were found in the breast cancer population.
The possibility of identical pathogenesis is debatable.

606P Local Tumor Invasiveness is more important prognostic factor than IPI in stage I_E/II_E extranodal NK/T-cell lymphoma, nasal type

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Background: Extranodal NK/T-cell lymphoma, nasal type (NTCL) is a subtype of non-Hodgkin's lymphoma, which arises from upper aerodigestive tract (nasal) or extranasal sites (extranasal). Unlike other subtypes, the tumor is locally invasive and Ann Arbor stage did not reflect prognosis correctly. Thus, we evaluate importance of local tumor invasiveness and International Prognostic Index (IPI) as a prognostic factor in NTCL.
Materials & Methods: Ninety-nine new patients were enrolled from 1992 to 2003. Among them, 77 showed nasal presentation and 22 presented at extra-nasal sites. Of 77 nasal NTCL, 63 patients showed stage I_E/II_E and 14 patients showed stage III_E/IV_E. Local tumor invasiveness of nasal NTCL is defined as follows: bony invasion/destruction or perforation or invasion to the skin. Nasal I_E/II_E NTCL patients were grouped into limited and extensive according to local tumor invasiveness.
Results: Patients' mean age was 47 years and male: female ratio was 1.8:1. Extranasal involvement (extranasal presentation and nasal III_E/IV_E patients) showed poor prognosis as compared with nasal I_E/II_E NTCL (8.8 months vs. 36.1 months: p=0.0072). In nasal I_E/II_E NTCL, Ann Arbor stage did not predict survival correctly (stage I_E, 36.1 months; stage II_E, 64.8 months). However, patients with limited local tumor showed longer survival than extensive involvement (104.0 months vs. 10.9 months; $p<0.0001$). IPI also showed predictive value (IPI 0~1, 64.8 months; IPI ≥2, 17.6 months; p=0.0307). Multivariate analysis showed local tumor invasiveness is the most significant prognostic factor in nasal I_E/II_E NTCL ($p<0.001$, Odds ratio 5.3, 95% CI 2.5~10.9).
Conclusion: Tumor invasiveness is more significant prognostic factor than Ann Arbor stage or IPI in nasal I_E/II_E NTCL.

607P A retrospective analysis of the clinical profile and induction outcome for acute myeloid leukemia at a tertiary care center in a developing country

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Objectives: To analyse the clinical profile and induction outcome in acute myeloid leukemia (AML) at our center, a tertiary care referral center for the state of Andhra Pradesh in India.
Database: About 100 new patients of AML are seen every year. This analysis includes 200 consecutive patients presenting from 1 Jan 2002 to 31 December 2003. Only about 46% of these underwent induction chemotherapy, due to financial constraints. The record contain all the demographic features, presenting signs and symptoms, the investigative work up including complete blood picture, biochemistry, marrow aspiration and biopsy, cytochemistry and karyotyping. Our typical induction over the entire period consisted of cytosine arabinoside 100mg/sq m as continuous intravenous infusion over 24 hours daily for 7 days along with mitoxantrone 10mg/sq m daily as short intravenous infusion for the 1st 3 days. We used blood components and antibiotics as need demanded - both prophylactically and therapeutically.
Results: There was a male preponderance - 59% were men. Most of our patients were between 21- 60 years (61%). Only 5% were over 60 years. Anemia was the commonest presentation (97%0. The white blood cell count was > 10,000/cu mm in 49% patients. The platelet count was < 50,000/cu mm in 67% of patients. AML-M2 was the commonest subtype (38%) followed by 20% AML-M4 and 18% AML M3. Of the 46% patients who underwent induction, complete remission was documented in 31%. Partial remission and refractory disease accounted for 39%. The induction mortality was 30%. Infection was the commonest cause of death.
Conclusion: The results of our center reflect the treatment outcome with this group of patients using this protocol - similar to other centers in India. They are however, far inferior to that observed in the western world. The results could probably be improved with better supportive care and alternative induction regimens.

608P Lymphoblastic lymphoma - a review of 56 cases from India

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Lymphoblastic lymphoma is a very aggressive form of non-Hodgkin's lymphoma (NHL). It often occurs in young patients, and is commonly associated with large mediastinal mass and a high predilection for dissemination to bone marrow and the central nervous system (CNS).
Aim: To study the clinical presentation, treatment and survival in patients with lymphoblastic lymphoma in a developing country.
Methods: 56 patients with a diagnosis of lymphoblastic lymphoma form the subjects of our study. These patients were seen, treated and is being followed up by us at Regional Cancer Centre, India, during the period 1994-2001. The patient records were studied in detail regarding the presentation, staging, treatment and follow up.
Results: Among the 56 patients, there were 39 males and 17 females. The age ranged from 14 years to 60 years (median 20 years). The commonst presentations were lymphadenopathy, dyspnoea, chest pain, pallor and SVC obstruction. B symptom was present in 31 patients. The median duration of symptoms was 6 weeks. Organomegaly was seen in 14 patients. Nine patients had a Haemoglobin less than 10 gms/dl, and 10 patients had a platelet count less than 1,00,000/mm^3. Serum LDH was elevated in 28 patients. Chest radiograph showed mediastinal mass in 20 patients, pleural effusion in 10 patients, and hilar nodes in 4. Para aortic lymphadenopathy was present in 11 cases. Bone marrow was involved in 17 patients. Among the 56 patients, 48 patients received treatment, 7 refused and one child died before we could start the specific chemotherapy. Multicentric protocol (MCP) designed by NCI for developing countries was used in the treatment of these patients. Twenty seven patients received MCP 841 (ALL protocol), and 18 patients received MCP 842 protocol (for marrow negative lymphoblastic lymphoma). Three patients received only VCR, Cyclophosphamide and steroids with intrathecal methotrexate in view of their old age. Twelve patients died, 33 patients are alive in remission, and 3 with disease at last follow up. Median survival of the series is 36 months (range 1-120 months), and 19 patients are alive beyond 48 months.
Conclusions: Lymphoblastic lymphoma, an aggressive lymphoma seen in adolescent males is curable with aggressive chemotherapy.

609P Relevance of molecular remission for clinical outcome in patients with follicular lymphoma. Single center experience

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Background: Follicular lymphomas (FL) are indolent lymphomas. FL cells carry the translocation t(14;18)(q32:q21) in about 80% of patients(pts). This translocation involves MBR or mcr region of BCL2 locus and IgH locus. First-line chemotherapy(chth) in FL results in clinical remission lasting a year or two. FL is difficult to eradicate. Even pts achieving a clinically complete response have malignant cells circulating in peripheral blood or residing in the bone marrow - residual disease (RD). A sensitive method detecting RD is polymerase chain reaction (PCR). PCR negativity in the presence of t(14;18) at diagnosis is called molecular remission.
Aim: The aim of this study was to investigate the correlation between clinical and molecular response in pts with FL.
Methods: 34 consecutive FL patients were seen at our center between 2000 and 2002. Using nested PCR we detected the presence of t(14;18) in peripheral blood and bone marrow in only 15 of 34 cases (44%). This group was selected for monitoring RD by PCR. The median age was 47 years (range 30-61), 4 pts were male, 11 female. Ann Arbor stages were III-IV -10 pts. WHO classification of pathological material was: G1 - 7 pts, G2- 4 pts, G3 - 1 pts, not known - 3 pts. BCL2 breakpoint in the MBR region was identified in 14 pts, mcr region in 2 pts. Both MBR and mcr breakpoints were present in 1 patient. Pts received various kinds of treatment (COP, R-COP, CHOP,R-CHOP,DHAP). 6 pts underwent autologus stem cell transplantation.
Results: 1 patient achieved complete response with RD detected in peripheral blood. 1 patient had a partial response with evidence of RD in peripheral blood. 1 patient after clinically complete response and molecular remission had recurrence of lymphoma with molecular relapse 6 months after finishing treatment. She died because of disease progression. The other 13 pts achieved complete clinical response and molecular remission. They are in good condition, with no clinical evidence of disease and sustained molecular remission with follow-up of about two years.
Conclusion: Detection of t(14;18) by PCR in our group was lower than reported by others. Monitoring BCL2 rearrangement in peripheral blood and bone marrow in our group strictly correlated with clinical outcome.

610P Ga-67 uptake: A predictor of active minimaly residual disease and clinical outcome in patients with diffuse large cell lymphoma

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Background: Most of the patients with diffuse large cell lymphoma (DLCL) can achieve complet remission (CR) after multidrug therapy, but evaluation of the presence or absence of a MRD following treatment stil represents a difficult diagnostic problem. So, 67Ga scan has been considered a good technique for monitoring response after treatment of patient with lymphoma.
Aim: The purpose of this study was to investigate 67Ga scan performed after treatment as a means to predict active minimaly residual disease and outcome in patients with DLCL.
Methods: Sixty-three patients with DLCL were studied with CT and 67Ga scan at the end of intensive chemotherapy.
Results: After treatment, 29 patients had a negative restaging CT. Of these patients, 15 had a positive 67Ga scan, 9 of whom (60%) relapsed; 14 had negative 67Ga scan of whom 1 (7%) relapsed. The 5-year relapse-free survival rate was 92% for those with negative scans compared with 33% for gallium-positive patients ($p < 0.001$). At the same time, 34 patients had a positive restaging CT. Of these patients, 17 had a positive 67Ga scan, 13 of whom (76%) relapsed; 17 had negative 67Ga scan of whom 5 (29%) relapsed. The 5-year relapse-free survival rate was 70% for those with negative scans compared with 23% for gallium-positive patients ($p < 0.004$).
Conclusion: 67Ga scan after intensive chemotherapy is a good predictor of active minimaly residual disease and clinical outcome of patients with DLCL.

611P Age and hemoglobin level emerge as the most important clinical progostic parameters in patients with osteomyelofibrosis: Introduction of a simplified prognostic score

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Background: Several prognostic models for patients with myelofibrosis with myeloid metaplasia (MF) have been developed, with the LILLE score now most commonly used. The latter and other previous scoring systems, however, fail to consistently separate patients with intermediate and poor prognosis. In this study we re-evaluated previous prognostic models and developed an improved prognostic score for patients with MMM.
Methods: We have studied 107 patients with MF and correlated clinical parameters at the time of diagnosis with survival by multivariate analysis. First, previous prognostic models were evaluated in our cohort of patients. Subsequently, an improved prognostic model was developed in a randomly selected training group and validated in a test group.
Results: Surprisingly, however, most previous scoring systems failed to clearly separate an intermediate and poor prognostic group, including the LILLE model. Instead, age and hemoglobin level emerged as most significant parameters in multivariate analysis. By allocating one risk point each for Hb<10 g/dL and age>60 years, three subgroups of patients with distinct prognosis could be identified in our cohort. The overall model and the difference between each of the subgroups were statistically significant in a training group, a test group, the overall cohort of patients and the group of patients with chronic idiopathic myelofibrosis.
Conclusion: We confirm that the LILLE and most other scores do not significantly separate the intermediate from the poor prognostic group of patients in MF. We propose an alternative prognostic model for patients with myelofibrosis which reliably identifies three groups with highly different outcome.

612P Dermatologic side effects of Imatinib mesylate corelate with cytogenetic response in CML patients from India

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We have prospectively evaluated a total of 240 patients with CML who were treated with Imatinib between May 2001 and May 2004. There was lightening of the skin color (hypopigmentation) in 158 of the 240 patients (66%) - the effect being seen in previously treated and de novo patients (i.e. with no previous exposure to hydroxyurea or any other chemotherapy). Development of hypopigmentation correlated with cytogenetic response. Major or complete cytogenetic response was seen in 71 of the 158 patients (45%) with generalized hypopigmentation in contrast to only
22 of the 82 patients (27%) without hypopigmentation (p = 0.01). Dermatitis was seen in 61 patients (25%).
Of these, 12 patients had Grade I, 39 had grade II and another 10 had grade III toxicity. In all patients with Grade I and 21 with Grade II dermatitis, topical steroids resulted in resolution of the skin lesions without need to discontinue imatinib. Imatinib had to be discontinued in 19 patients with grade II toxicity, following which there was complete response to continued topical steroids. Systemic steroids were used for all 8 patients with grade III toxicity - with response in all of them. Imatinib could be restarted in all of them - without reappearance of dermatitis.
Of the 49 patients with grade II/III toxicities, 44 patients were males (90%) and only 5 were females (10%) (p = 0.001). Sixteen (33%) of these 49 patients achieved major cytogenetic response as compared to 80 of the 191 patients (42%) with no or grade I dermatitis (p=0.148). Dermatitis was not related to the dose of imatinib (400mg Vs 600-800 mg, p=0.187).
We conclude that hypopigmentation and dermatitis correlates with cytogenetic response to imatinib in patients with CML from India.

613P Interleukin-10 and IFN-γ cytokine gene polymorphisms can be risk factors for chronic myelogenous leukemia

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Chronic myelogenous leukemia (CML) is a myeloproliferative disease characterized by a proliferation of myeloid cells without loss of their capacity to differentiate. Cytokines play crucial roles in the regulation of immune response. The cytokine production capacity varies among individuals and depends on the cytokine gene polymorphism. In the current study we investigated the association of cytokine gene polymorphisms with the development of CML and whether there is an association between gene polymorphisms Th1, Th2 or regulatory type cytokines and CML.
The study included 30 patients with the diagnosis of CML and 60 healthy controls. All genotyping (TNF-α, TGF-β, IL-10, IL-6, IFN-γ) studies were performed using sequence-specific primers PCR (PCR-SSP).
The cytokine genotyping results of the patients were compared to those of the healthy controls. It was found that IL-10 (-1082, -819, -592) GCC/ATA (*P*= 0.009), IFN-γ + 874 T/A (*P*=0.037), polymorphisms were significantly higher in the CML group than in the healthy control group. In contrast, significantly lower frequencies of IFN-γ A/A (*P*=0.004) genotype were observed in the patient group in comparison to controls.
The results suggest that IL-10 GCC/ATA, IFN-γ T/A, polymorphisms are potential risk factors, IFN-γ A/A polymorphism is a protective factor for CML in the Turkish population. In conclusion, we have demonstrated an association between certain cytokine gene polymorphisms and CML in the Turkish population. Our results provide information for further clinical trials in large series of CML patients. To our knowledge, this study provides the first evidence for a genetic association between CML and the cytokine genes.

614P The significance of P53 and Bcl-2 protein expression in patients with primary gastrointestinal diffuse large B-cell lymphomas

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Background: In recent years, it was found that mutations occurring in apoptosis-related gens have important roles in the pathogenesis and course of lymphomas and also was found related with drug resistance, treatment response and decreased survival.
Aim: We investigated the effect of expression aof poptosis-related proteins such as P53, Bcl-2 and Fas protein on the clinical course, treatment response and also prognosis in the patients with primary gastrointestinal diffuse large B-cell lymphoma.
Methods: A total of 39 patients, whom had diagnosed in Erciyes University Department of Pathology and whom had followed at Hematology Department between January 1992 and September 2003 were included in our study. In the sections obtained from paraffin blocks, P53, Bcl-2 and Fas protein expression was showed with immunohistochemical methods.
Results: P53 protein expression was determined in 24 of the patients (61,5%), Bcl-2 protein expression in 26 (67%) and Fas protein in 28 (72%). While 5-year overall survival (OS) was found 17%, disease free survival (DFS) 34%, event free survival (EFS) 44% in patients with p53 protein expression; it was found 68%, 85% and 85% respectively in patients with no protein expression and this was statistically significant. While 5-year OS was 23% in patients with Bcl-2 expression, it was found 59% in patients with no Bcl-2 expression, this was statistically significant. However, in patients with Bcl-2 expression, while 5-year DFS was 44%, EFS 51%, it was 83% and 85% respectively in the patients with no protein expression and there was no statistically significance. While 5-year OS was 33%, DFS 58%, EFS 54% in patients with Fas expression, it was found 36%, 75% and 75% respectively in patients with no protein expression and there was no statistically significance among them. P53 and Bcl-2 protein expression rate was found higher in patients whom was Ann-Arbor advanced stage and also whom had high-intermedium and high International Prognostic Index (IPI) scores.
Conclusion: Lymphoma patients with an expression of apoptotic gen related proteins such as P53 and Bcl-2 are in high-risk and these patients should be treated by aggressive chemotherapy.

615P HHV-8 plasma viral load (VL) in HIV associated lymphoproliferative diseases

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We evaluated the HHV-8 VL and HIV infection in: 8 patients (pts) affected by Multicenter Castleman Disease (MCD), 4 with primary effusion lymphoma (PEL) and 3 with HHV-8 positive solid lymphomas (SL) diagnosed and treated in our Institute. At the onset HHV-8 VL was measurable in all 3 groups and the median value was 4400 (range $6x10^2$-$1.6x10^6$), 12700 (range $2.9x10^2$-$8.0x10^4$) and 555000 cp/ml (range 5.1 $x10^5$-$5.4x10^6$) in MCD, PEL and SL, respectively. MCD pts had a median value of CD4 count of 327/mm^3 (range 55-424), PEL of 43/mm^3 (range 25-839) and HHV-8 of 104/mm^3 (range 20-282). HIV-viremia was undetectable in 3/7 pts in MCD group, in 3/4 PEL pts and only in 1/3 HHV-8 SL. All pts had positive serology for EBV. EBV-plasma DNA was measurable in all pts with PEL and SL, and only in 3/8 MCD pts. In PEL pts, HHV-8 had a significantly negative correlation with CD4 count (r=0.80). In MCD EBV plasma DNA was significantly lower level than in PEL and SL (p=0008, p=0.01). The HHV-8 VL was lower in MCD pts than in PEL pts (p= 0.07) and significantly lower than SL pts (p=0.02). Four out of 8 MCD pts were treated only with HAART and 5 with oral VP16 and HAART, the median overall survival (OS) was 44 mos, 3 PEL pts were treated with CHOP-like regimen and HAART and 1 with HAART alone the median OS was 18 mos. The 3 SL pts were treated with CHOP-like regimen with a poor outcome: OS $<$1 mo. We found that pts with HHV-8 $>$40000 cp/ml had a shorter OS when considering all diseases together. The same trend is present in each distinct diseases. MCD has the better prognosis and it is associated with higher CD4 count with a lower HHV-8 VL while SL have the worst outcome and the highest level of HHV-8 VL. HHV-8 VL might be a prognostic marker in this setting.

616P Haemopoiesis restoration in sternal bone marrow after low dose accelerated hyperfractionated radiotherapy for mediastinal Hodgkin's lymphoma

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Background: Conventional irradiation to 40 Gy produces permanent ablation of exposed bone marrow. It may cause problems with adequate stem cells harvesting when high dose chemotherapy becomes necessary.
Purpose: Our aim was to evaluate whether bone marrow haemopoiesis may be preserved when low-dose radiotherapy is delivered in accelerated hyperfractionated regimen (LDAHFX).
Materials/Methods: Therapeutic benefits of LDAHFX (1,3-1,5 Gy twice daily to 20-22 Gy) against conventional 40 Gy for control of bulky or residual disease have been investigated in a series of clinical trials of combined modality therapy for HL I-IY stages. 120 patients received LDAHFX between 2nd and 3rd COPP (total 6) cycles, or after 6 x COPP/ABV or ABVD or BEACOPP regimens. Bone marrow aspirates were obtained from an exposed sternum and evaluated for total myelokaryocyte count, as well as for CFU-GM and CFU-F concentration. Investigation started 4 month posttreatment; 14/15/15 pts were examined at follow-up visits of the 1st, 2nd year and later, respectively.
Results: During first two years the median myelokaryocyte content ($x10^9$/l) was increased from 20 (range 6-54) to 36 (range 8-150) without further changes. Concentration of CFU-GM and subpopulations of CFU-F, forming in culture dense or sparse colonies of fibroblasts clones, were evaluated 4-12 (median 5) months post treatment in a group with LDAHFX between COPP cycles (n=9). In these patients, relatively low cellularity ($30\pm11x10^9$/l) at first year was associated with preserved functional capacity, judging from CFU-GM and CFU-F evaluations. Since 2nd year, mean cellularity ($x10^9$/l) of bone marrow exposed to LDAHFX was similar in pts after COPP (43 ± 9), BEACOPP (44 ± 10) or ABVD (50 ± 7) regimens. Thus no evident explanation was found so far to the fact of low cellularity after COPP/ABV regimen (19 ± 3 vs 45 ± 5, p=0,01).
Conclusion: Functional capacity and supportive function of bone marrow stroma were restored during first year after low dose AHFX. Myelokaryocyte content increased by second year to the extent depending on CT regimen at use.

617P New translocation t(11;17)(q11;q11) leading to a dicentric chromosome in AML FAB M6

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In March 2004, this previously healthy 48-year old man was admitted to our hospital because of increasing fatigue, fever up to 39°C, cough and night sweats during the past weeks. Physical examination and chest x-ray were unremarkable. Peripheral blood count was as follows: haemoglobin 7,4 g/dl, platelets 32 $\times$ 10^9/L, white blood cells 5,6 7times; 10^9/L with 10% myeloid blasts. Routine laboratory values with exception of the lactate dehydrogenase (497 U/L, normal below 225 U/l) and slightly elevated transaminases were normal. Bone marrow aspiration showed a 24 percent infiltration by myeloid blasts. Megaloblastoid erythropoiesis was markedly increased by proerythroblasts with vacuolated cytoplasma, positive for PAS-staining. Immunophenotyping demonstrated erythroblasts to be positive for glycophorine A and CD36 and myelomonocytic cells to be positive for CD14, CD4, CD13, CD33 and CD36. According to these findings acute myeloid leukemia FAB M6 was diagnosed.
Cytogenetic investigation showed the following complex karyotype: 42-46, XY,del(3)(q11),del(5)(q31), dic(11;17)(q11;q11), -13,-21,-22,+2 mar[4].
Additional FISH-analyses with painting- and α-satellite-probes for chromosomes 11 and 17 confirmed the dicentric nature of the derivative chromosome. Interestingly, we found two signals for P53 with a probe, specific for 17p13, suggesting that the p-arm of chromosome 17 is not lost, but is contained in one of the marker chromosomes.
Translocations of chromosomes 11 and 17 are described in 11 cases of AML with various FAB subtypes, but to the best of our knowledge so far no dicentric chromosome has been found. Whether this new translocation is of prognostic impact has to be studied in the future.

618P The expression of CD56 on malignant plasmocytes and bone disease in patients with multiple myeloma

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Osteolytic lesions and osteoporosis are among the principal causes of morbidity in multiple myeloma (MM). CD56 (NCAM - neuronal cell adhesion molecule) is a molecule that has a role in interactions between cells and between cells and extracellular matrix. The objective of this study was to evaluate the correlations between the expression of CD56, bone disease, and selected biochemical and clinical parameters in MM. The study included 35 patients with newly diagnosed MM and 12 patients with relapse or progression of the disease. The expression of CD56 was detected in bone marrow biopsies using a monoclonal antibody. Malignant plasma cels expressed CD56 in 74.5% of the patients. No statistically significant differences in selected biochemical markers (beta2-microglobulin, calcium, albumin), bone marrow infiltration, age, gender, myeloma type and stage (Durie-Salmon and IPI) have been found between the CD56+ and CD56- groups. The expression of CD56 correlated significantly with the presence of osteolytic lesions detected by x-rays (p=0.0006) and with the occurrence of bone events (pathologic fracture or a bone lesion requiring paliative radiotherapy or surgical intervention) (p=0.0339). Thus, CD56 is a useful marker that closely correlates with the presence of bone disease in patients with MM. In contrast to standard imaging, the expression of CD56 is related to certain intrinsic properties of malignant plasmocytes and, therefore, can predict the clinical course of myeloma bone disease.
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619P Expression of death associated protein kinase 2 (DAPK2) during myeloid differentiation, a gene selected through differential gene expression profiling

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Myeloid differentiation is a complex process governed by orchestrated regulation of many different genes. We were interested in identifying new genes involved in both normal and leukaemic myeloid differentiation. The promyelocytic HL-60 and t(15;17)+ NB-4 leukaemic cell lines were differentiated *in vitro* with all-trans retinoic acid (ATRA) towards granulocytes, and with phorbol ester myristate (PMA) to monocytic-like cells. Gene expression profiles were obtained by DNA oligonucleotide microarrays (Affymetrix U133 A) which contain 24'000 human genes. NB-4 cells treated with ATRA (1μM during 6 days) showed a particularly pronounced (4000x) up-regulation of DAPK2 mRNA, confirmed with Real time Quantitative RT-PCR (RQ-PCR), and an increase of DAPK2 protein expression in Western blots. Likewise HL-60 cells treated with PMA (10 ng/ml, during 3 days) showed an up-regulation of DAPK2 mRNA (800x in RQ-PCR), as well as increased in protein expression. Differentiated myeloid cells expressed variant DAPK2 transcripts on Northern blots. Furthermore, Western blots revealed differentially expressed protein variants in the nucleus and the cytosol, respectively. In keeping with results from cell lines, fresh neutrophil granulocytes and monocytes showed high DAPK2 expression levels whilst expression of DAPK2 in undifferentiated CD34+ progenitor cells, and in patient samples from various types of AML was low.
DAPK2 is a 42-kDa Ca2+/Calmodulin-regulated serine/threonine kinase acting as a positive mediator of apoptosis. Our data now show, that the gene is highly expressed in differentiated neutrophil granulocytes or monocytes, whilst AML samples, and CD34+ progenitor cells show low DAPK2 expression, which further supports its possible functional involvement in myeloid differentiation and in the maturation block seen in AML. DAPK2 has so far never been identified as being involved in normal or leukaemic myeloid differentiation. Further experiments planned to elucidate its role include *in vitro* differentiation of CD34+ cells towards monocytes and granulocytes, and blockage of induced DAPK2 up-regulation by small interfering RNAs.

620P Relation of Epstein-Barr virus in pheripheral T-cell lymphoma, unspecified (PTL, unspec)

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Introduction: Peripheral T-cell lymphoma, unspecified, is often of poor outcome; however the presence of Epstein-Barr Virus is related to worse prognosis.
Material and Methods: From 1988 to 2000, 40 new cases of peripheral T-cell lymphoma were diagnosed in the Instituto Especializado de Enfermedades Neoplásicas "Dr. Eduardo Cáceres Graziani" Lima-Perú. The biopsies samples were analyzed with an *in situ* hibridization assay to EBV (DAKO). Individual groups EBV (+) and EBV (-) were analyzed, and the comparison of clinical characteristics, International Prognostic Index, regime of treatment and response to treatment, recurrence or progression of the illness, survival and overall survival in both groups were evaluated.
Results: 11 EBV (+) patients (28%) and 29 EBV (-) patients were founded. There were no difference between clinical characteristics, International Prognostic Index, regime of treatment and response to treatment ($P > 0.05$). However, it was observed that the EBV (+) patients had a worse rate of 5-year overall survival (27%) compared EBV (-) (33%), but without significant differences.
Conclusion: These data suggest that evolution of EBV (+) PTL, unspec patients has a similar outcome to EBV (-) PTL, unspec patients; although the latter presents a higher survival, this is not significant.

621P Megakaryocytopoiesis in clean-up workers of the Chernobyl accident with myelofibrosis with myeloid metaplasia

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Background: It is well known that marrow fibrosis in myelofibrosis with myeloid metaplasia (MMM) is characterized by dysplastic features of megakaryocytes, high levels of growth factors being released by increased number of megakaryocytes. Features of MMM developed after exposure to ionizing radiation (IR) has not been studied before. It is of interest because IR can stimulate fibroblasts proliferation and lead to myelofibrosis development by itself. The aim of the study was to evaluate the Megakaryocytopoiesis in MMM developed in clean-up workers of the Chernobyl accident exposed to IR in the range of 0.01-0.25 Sv.
Material and methods: We studied 52 MMM patients. Of those, there were 29 clean-up workers and 23 patients who have not been exposed to IR (control group). Morphology of megakaryocytes was analyzed on bone marrow smears stained by Pappenhaim. The differential count was done on 100 megakaryocytes for each case. The significance of the differences between group means was assessed by the Student t-test.
Results: Clean-up workers with MMM had significantly decreased number of polychromatophilic megakaryocytes accompanied by their lower functional activity and high content of hypolobulated forms than patients of control group ($p<0.05$). At that, clean-up workers with MMM had significantly increased the total number of oxyphilic megakaryocytes ($p<0.05$). Oxyphilic megakaryocytes tended to be functionless. It was characteristic that the megakaryocytes of all maturation stages in patients previously exposed to IR are less functional active. The patients in control group more often had megakaryocytes with picnotic nuclei with active platelet formation ($p<0.05$) and higher mean number of platelet in peripheral blood ($p<0.05$). Megakaryocytes in clean-up workers with MMM demonstrated much higher rate of dysplastic features ($p<0.05$), and more often had vacuoles ($p<0.01$).
Conclusions: Common peculiarities of megakaryocytopoiesis in MMM developed in clean-up workers of the Chernobyl accident are differentiation delay, dysplastic features and alteration of maturation. The further studies are needed to specify the role of IR in the formation of the disease.

622 Ten years follow up of aggressive non-Hodgkin's lymphoma patients treated with ACVBP/MXT-CAR regiment

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Background: ACVB regimen was created by GELA group in the late 1980s, and has been evaluated since 1989 (CRR 75%, TTF at 2 years, 67%, OS at 2 years 67%). Modified ACVB was compared with standard CHOP in 2002 (CRR 58% vs. 56%, P=0.5, EFS at 3 years, 46% vs. 33% P =0.02, OS at 3 years, 53% vs. 45% P=0.03).
Aims: The aim of study was to evaluate the therapeutic contributions of the modified ACVB regimen (higher doses of vincristine and bleomycin in inductional therapy and use of another anthracycline drug, mitoxantrone in consolidation therapy).
Patients and methods: Between October 1992 and April 2002 25 patients (M/F:13/12; age: med: 49 years, range 18-69 years), with aggressive histology (WF: E1, F5, G12, H3, other 4), and in advanced clinical stages (AA: I X 2, II 4, IV 19), were treated with ACVBP (DOX 75/m^2 - I, CPM 1500 mg/m^2 - I, VCR 2 mg - and V, BLM 10 mg/m^2 - I and V, PDN 60 mg/m^2 - I to V; q29 days), with or without G-CSF as a primary prophylaxis (randomisation), and responding patients (CR/PR) were treated with consolidation therapy MXT-CAR (MXT 10 mg/m^2 - I, CAR 1000 mg/m^2/q12 hours I and II, q29 days). Three cycles of ACVBP and two cycles of MXT-CAR were included in the original schedule.
Results: ORR 15/25 (60%), CRR 15/25 (60%), SD/PD 9/25 (36%), NE 1/25. TTP probability at 10 years P=0.45, plateau curve at 36 months. OS probability at 10 years was P=0.24, plateau curve at 12-75 months.
Hematologic toxities (from 63 cycles): Hb gr. III/IV - 5/63, Le gr. III/IV - 28/63, Tr gr. III/IV 6/63. Le gr. III/IV (G-CSF vs. no-G-CSF) $P<0.01$.
Non-hematologic toxities (from 63 cycles): infection gr. III - 2/63, peripheral neuropathy gr. III - 1/63, BUN gr. III - 1/63, circulatory gr. III - 1/63. TRD: 2/25 (thrombocytopenia gr. IV and hemorrhagic schock, BUN gr. III and kidney failour).
Secondary malignancies: 3/25 (HGL Ph positive - 59 months, HGL Ph negative - 55 months, AML FAB/M3 - 12 months).Conclusions: The ACVBP/MXT-CAR regimen is effective and feasibile, especially with G-CSF as a primary prophylaxis. Probability of 10 years overal survival (p=0.24) compared with historical controls (meta-analysis - Missori A. et al, Brit J Cancer 2001; 84: 3) is comparable with probability levels reported for third generation regimens and CHOP (P=0.23 and P=0.26).

623 The results of treatment Hodgkin's lymphoma in children

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During last decade there have been a lot of changes in strategy of treatment Hodgkin's disease (HD) in children. According to very good reaction of chemotherapy we are trying to find out the stage and subtype of a disease, and the use the less aggressive but very effective therapy which will cure a large number of patients with less side effects. It is very well known that secondary malignant tumours are very frequent after successful therapy of HD. Chemotherapy has the leading role in treatment this disease but we must say that this treatment is much less toxic than before. Radiotherapy is used with fewer patients.
The aim of this report is to give treatment results of children with HD in Croatia. They were staged and treated in a single institution.
Patients and Methods: At the Department of hematology and oncology Children's Clinic Salata Medical Faculty Zagreb, in the period of 1990 - 2003, 41 children (19 male and 22 female, 2 - 18 years) with HD have been treated with combination of cytostatic therapy (OPPA,OEPA and COOP) and radiotherapy (involved field radiation); 6 were in stage IA, 13 in stage IIA, 11 in stage IIB, 5 in stage IIIA, 3 in stage IIIB and 3 in stage IVA.
Results: The remission has been achieved in all patients; in 5 (12.2%) relapse appeared due to which considerably more aggressive cytostatic therapy as well as radiotherapy were applied; in 3 (7.3%) in combination with bone marrow transplantation; 2 (4.9%) patients died. 39 (95.1%) patients are alive in the 1st or the 2nd remission. Serious side effects were not noticed. Secondary malignancies did not occur in any of patients.
Conclusion: The results of treatment are not different from the other European Centres for children's hematology and oncology.

624 Institution of the protocol Vincristin.Adriamycin. Dexamethason (V.A.D) for home care by the university hospital of Amiens

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Introduction: The V.A.D protocol is an intravenous polychemotherapy used

as an alternative is to melphalan in order to treat myeloma with big tumoral mass (grade 3) in patients in good condition.
Methods: The reconstitution of chemotherapies is made up by centralized facility for the reconstitution of anticancer drug. Dosages are 9 mg/m^{2}qs 100 ml physiological salt solution for doxorubicin and 0.4 mg/m^2 qs 100 ml physiological salt solution for vincristin. Packaging reservoir cassette form graseby® included in an infusion pump graseby® 9300 PCA will allow a 24 hour continous infusion (i.e. a 4ml/hour out flow). The duration of the anticancerous course of treatment is four days. Dexamethason per os is combined, 40 mg pd with that infusion.
Result: This treatment presents advantages: fewer adverse effects, home care, reduction of the nurse workload, faster turn over of patients in the hospital and drop in the cost of treatment (no hospitalization)
Conclusion: At the moment, this way of doing begins to be applied. It opens prospects for other anticancerous drug (e.g. aracytin). It allows to further the home care and to drop the health spending.

625 Clinical profile and outcome of extranodal non-Hodgkin's lymphoma: Experience of a regional cancer centre in the South Asian subcontinent

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Aims and objectives: An in-depth analysis of the clinical profile and to analyze the outcome of the treatment of extra nodal NHL.
Material and methods: 73 cases of extra nodal lymphomas presenting at Gujarat Cancer & Research Institute, Ahmedabad, India from March 2001 till February 2003 were analysed prospectively.
Observations: (a) IPI scores and relation to CR rates & outcome

Site	IPI score	No of cases	Attained CR	Status at last F/U
	0/1/2	6	6	4 Ir CCR
GI tract (18 cases were evaluable)	3	7	3	1 Ir CCR, 3 alive with disease
	4	3	1	1 CCR 1 alive with disease
Head & neck (10 cases were evaluable)	0/1/2	8	7	5 Ir CCR, 1 alive with disease
	3	2	1	Disease progression in both
Bone (8 cases evaluable)	0/1/2	5	5 (PR 1)	4 Ir PR1
	3/4/5	3	2	2 Ir PR1
	0/1	2	2	2 Ir CCR
GU tract (3 cases were evaluable)	2	2	1	None in CCR, 1 alive with disease
	4	2	None	None
Skin (1 case evaluable)	4	1	1	Disease progression
Mediastinum (4 evaluable)	3	4	3	None in CCR, 3 alive with disease
OVALUABLE	0/1/2	28	23 (82%)	18 Ir CCR (78.3)
4T cases	3/4/5	22	11 (50%)	4 Ir CCR (16.6%)

CCR=continued complete remission; F/U=follow-up; PR=partial response
Table no. 6: Overview: outcome of extranodal lymphomas (evaluable)

NHL Sites	Evaluable cases	CR rates	Median FU time in months	DFS (no. cases)	OS (no. cases)
G.I.T.	15	86.6%	17	60% (9)	73.3% (11)
HNN	1	[illegible]	16	50% (1)	100% (1)
PLB	0	37.5%	17	75% (3)	75% (3)
G.U.T	6	50%	17.5	33.3% (2)	50% (3)
PCNSL	3	100%	14	33.3% (1)	33.3% (1)
HIV related	4	100%	16	75% (3)	75% (3)
Splenic	1	100%	22	100% (1)	100% (1)
Skin	1	100%	12	100% (1)	100% (1)
mediastinal	4 cases	75%	16	50% (2)	50% (2)
Overall	55 cases	76.4%	17	49% (27)	69% (38)

Conclusions: G.I. tract NHLs were commonest (34.3%), followed by head & neck and bone lymphomas (together 35.6%). Male to female ratio was 1.7:1 and majority (46.6%) occurred in the age group of 20 to 49 years. The clinical manifestations corresponded to the primary site.The most common histologic variant was diffuse large cell lymphoma (60.3%) and majority (65.75%) were intermediate grade NHLs. 67 cases (91.8%) were B-lineage in origin. Treatment incorporated all the three oncological modalities. 55 cases were evaluable. 42 cases achieved complete remission (76.4%). With a median follow-up period of 17 months, the DFS (disease free survival) is 49% (27 cases) and the overall survival is 69% (38 cases). The International Prognostic Index scoring system truly reflected the induction of remission as well as the duration of remission. Patients with low/low intermediate IPI scores had higher CR rates (92%) and much higher continued CR rates (72%) than those with high intermediate/high IPI scores (CR in 52% only and continued remission in 18.18% only).

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626O A randomized phase III trial of tirapazamine (T) in combination with cisplatin (C) and vinorelbine (V) versus cisplatin and vinorelbine in advanced non-small cell lung cancer (NSCLC)

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Background: A plateau has been reached with cisplatin-based doublet regimens in the treatment of advanced NSCLC. Addition of a third agent is of unproven benefit. Tirapazamine, which is a cytotoxic drug targeted to hypoxic cells by virtue of a reduction mechanism, has been shown to add to cisplatin efficacy in this setting (CATAPULT I trial, JCO 2000). This trial compares TCV versus CV, one of the reference doublets in advanced NSCLC.
Methods: Inclusion criteria: Advanced NSCLC, Stage IIIB/IV, no CNS involvement, adequate renal, hepatic, and hematologic function, KPS >/= 70%. Patients on TCV received: Day 1, T (330 mg/m^2), followed by C (100 mg/m^2), followed by V (25 mg/m^2); Days 8, 15, and 22, V (25 mg/m^2). Each cycle was repeated every 4 weeks up to 6 cycles. Patients on CV received the same treatment without T.
Results: 414 patients were randomized to each arm from 8/00 to 2/02. The two arms were well balanced. The efficacy endpoints were not statistically different between the two arms. A higher frequency in the TCV arm occurred for: any AE (Gr 3/4), febrile neutropenia/sepsis, vomiting (Gr 3/4), nausea (Gr 3/4), diarrhea (all Gr), rash (all Gr), anorexia (Gr 3/4), and cramps (all Gr).
Conclusion: Tirapazamine does not improve the response rate or survival in advanced NSCLC but does add toxicities when added to a standard two-drug regimen, vinorelbine-cisplatin. As with other combinations, even those of different mechanisms of action, adding a third drug to a standard doublet gives more toxicity without survival benefit. Studies with tirapazamine in Head and Neck Cancer are continuing with early positive results.

Efficacy Endpoint	TCV n=414	CV n=414
Median OS in months	11	9.7
(95% CI)	(7.9-9.7)	(8.4-10.3)
CR (%)	4 (1.0)	7 (1.7)
PR (%)	132 (31.9)	129 (31.2)
Toxicity	TCV n=404	CV n=410
All Gr 3/4 [%]	300 (74)	310 (76)
Febrile neutropenia/sepsis [%]	55 (13)	53 (13)
Anorexia Gr 3/4 [%]	34 (8.4)	17 (4.1)
Cramps, eps All Gr [%]	105 (25.9)	14 (3.4)
Nausea Gr 3/4 [%]	64 (16)	42 (10)
Vomiting Gr 3/4 [%]	54 (13)	32 (7.8)

627O The impact of adjuvant vinorelbine (VIN) and cisplatin (CIS) on quality of life (QoL): Results from The National Cancer Institute of Canada Clinical Trials Group Trial BR.10 randomized trial of VIN/CIS versus observation in stage IB and II non-small cell lung cancer (NSCLC)

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Platinum based adjuvant chemotherapy using 2nd generation regimens increase cure by 4-5% in resected NSCLC. BR.10 tested whether the

3rd generation regimen VIN/CIS prolonged survival in this clinical setting. Patients with completely resected Stage I (T2N0) or Stage II (excluding T3N0) NSCLC and ECOG PS 0-1 were stratified by nodal and ras mutation status and randomized to receive 4 cycles of VIN (25mg/m^2 weekly x 16 weeks) plus CIS (50mg/m^2 days 1 and 8 q 4 weeks x 4) or follow up alone; VIN dose was reduced from 30mg/m^2 shortly after the study started due to unacceptable toxicity. The endpoints of the study were survival (OS), recurrence-free survival (RFS), QoL (EORTC QLQC30) and toxicity. QoL participation was mandatory for participating Canadian centres. 482 patients were randomized between 1994 and 2001. Patients: age 61 years, 65% male, 51% PS 1, 53% N1, 24% ras mutation present. 45% of patients had T2N0, 40% T2N1 and 15% T1N1. Grade 4 neutropenia, was common with febrile neutropenia in 7%. The commonest Grade 3 & 4 non-hematologic toxicities for VIN/CIS patients were fatigue (14%), nausea (10%), anorexia (9%) and vomiting (7%). Two patients died of drug-related toxicity [sepsis, pulmonary fibrosis]. Overall survival was significantly prolonged for VIN/CIS patients (94 months vs. 73 months; HR 0.69, p=0.012), as was RFS (not reached vs. 46.7 months; HR 0.6, p 0.0004). 38 patients developed 2nd malignancies. 72-73% completed baseline QoL assessments. As expected, treatment with VIN/CIS was associated with significant effects on QoL: patients had significantly worse global QoL, physical, role, social and cognitive function, as well as fatigue, nausea, dyspnea, anorexia and alopecia compared to patients on observation alone. However, after completion of VIN/CIS, only symptoms of parasthesia, numbness and hearing loss persisted. Treatment with 3rd generation platinum-based doublet adjuvant chemotherapy prolongs OS and RFS after surgery in early stage NSCLC and is associated with a significant, but generally reversible impact on QoL.

628O Epidermal Growth Factor Receptor (EGFR) and HER2 gene amplification predict response to gefitinib therapy in advanced non-small cell lung cancer (NSCLC)

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Background: Gefitinib is active in 12-18% of NSCLC. EGFR gene mutations were found in a subset of responding patients, but their low frequency in unselected patients suggests that other mechanisms are involved in gefitinib sensitivity. This study correlates EGFR and HER2 gene status with gefitinib activity.
Patients and Methods: EGFR and HER2 were evaluated by fluorescence *in situ* hybridization. One-hundred-eight NSCLC patients progressing or relapsing with standard therapy received gefitinib at a daily dose of 250 mg until disease progression, unacceptable toxicity, or refusal. Majority of patients were male (67%), PS 0-1 (85%), current or former smokers (85%) and median age was 62.1 years (range 25-83). Adenocarcinoma was the main histology (52%).
Results: High EGFR gene copy number (EGFR positive) represented by gene amplification (GA) or $\geq$4 gene copies in $\geq$40% of tumor cells was found in 32% of patients, and significantly related to female gender (p=0.037) and never-smoking history (p=0.001). In EGFR GA patients objective response (OR) was 53.8% and disease control rate (DCR) 76%. EGFR positive patients had significantly better OR (36.4% versus 2.9%, p$<$0.001), DCR (66.7% versus 26.1%, p$<$0.001), significantly longer time to progression (TTP: 6.3 versus 2.5 months, p$<$0.001) and survival (OS: 9.0 versus 6.5 months, p=0.03) than patients with no or low genomic gain (EGFR negative). HER2 GA was found in 10%, and was significantly related to female gender (p=0.01) and smoking history (p$<$0.05). Patients with HER2 GA had significantly better OR and DCR (60.0% and 70.0% versus 7.7% and 35.2%, p$<$0.001 and p=0.04), longer TTP (p=0.01), and a trend towards better survival (p=0.1). EGFR positive/HER2 GA patients had better OR (83.3% versus 1.5%, p$<$0.001) DCR (83.3% versus 24.6%, p=0.007), and longer TTP (p=0.002) compared to EGFR negative/HER2 non-amplified patients. Addition of HER2 GA to EGFR positive status resulted in better OR (p=0.01).
Conclusions: EGFR GA or high polysomy and HER2 GA are strong predictive factors for response to gefitinib therapy. Presence of HER2 GA confers a more sensitive phenotype to EGFR positive and a better outcome to EGFR negative patients.

629O Non-small-cell lung cancer (NSCLC) tumors from gefitinib-responsive patients (pts) harbor EGFR kinase domain mutations

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The potential relevance of EGFR mutations to NSCLC treatment has recently been identified. In the present study, laser capture microdissection was performed for the accurate procurement of tumor cells. EGFR exons 18, 19 and 21 and flanking intron sequences were amplified from genomic DNA by means of PCR, and the samples were then subjected to bidirectional automatic sequencing. So far, 34 gefitinib-treated pts have been screened, 18 from Japan and 16 from Spain, in addition to 1 cetuximab-treated Spanish pt and 1 untreated pt. Most of the female pts and non-smokers were Japanese, while there were more males and more smokers among the Spanish pts. The median number of prior chemotherapy regimens was 3 in the Spanish and 2 in the Japanese group (P=0.02). EGFR mutations were observed in 12.5% of the Spanish pts and in 41% of the Japanese pts (P=0.17). 7/9 Japanese gefitinib responders harbored EGFR mutations: 3 missense mutations at exon 18, and 4 in-frame deletions removing amino acids 746 through 750 (ELREA), one of which was a heterozygous in-frame deletion (747-751) and insertion of phenylalaline residue. The only Spanish gefitinib responder also harbored a heterozygous in-frame deletion (746-751) and insertion of alanine residue. Some of the other mutations were homozygous. Although no mutations were found in non-responders, one was found in a Spanish pt with stable disease who had two primary lung cancers. The mutation was found in the resected specimen of lung adenocarcinoma but not in the second relapsing primary squamous cell carcinoma. Missense mutations were also found in the untreated pt and in the cetuximab-treated responder (L861R). In Japanese pts, mutations were more frequently observed in pts $<$60 years (P=0.05) and in non-smokers (P=0.05). Median survival for Japanese pts with EGFR mutations was 15.6 months from the start of gefitinib treatment, while for the remaining Japanese pts with wild-type EGFR, it was 2.3 months (P=0.04). Sequencing analysis is being performed in additional Spanish, German and Chinese gefitinib-treated pts and in the gefitinib-sensitive human NSCLC cell line PC9. Since median survival of Spanish pts with stable disease was 14 months, other genetic alterations are being examined in these pts. EGFR mutations are present more frequently in Japanese, non-smokers, and pts $<$60 years, and can be used as a predictive marker for EGFR inhibition. In the meaningful number of non-Japanese pts with stable disease, other markers may predict the relatively good response to EGFR inhibition. Final data will be presented.

630PD A phase III study of docetaxel versus docetaxel plus gemcitabine in refractory non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy: Results of a Japan Clinical Oncology Group randomized trial (JCOG0104)

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Background: Docetaxel (D) is currently the standard second-line treatment for refractory NSCLC based on improved survival and quality of life in two randomized phase III studies. Docetaxel plus gemcitabine (DG) has also shown promising results against refractory NSCLC in several phase II studies. We conducted a randomized trial to evaluate whether combination regimen of DG provides better overall survival than D in patients with previously treated NSCLC.
Methods: Eligibility included histologically or cytologically proven NSCLC, stage IIIB or IV, one prior platinum-based chemotherapy, performance status of 0 to 1, 20-75 years old. Patients were randomized to receive either D (60 mg/m^2, day 1) or DG (D 60 mg/m^2, day 8, G 800 mg/m^2, days 1, 8), repeated every 21 days until disease progression.
Results: 65 patients were accrued in each arm from January 2002 to April 2003 (projected accrual; 142 per arm); two were ineligible due to stage IIIA.