doi: *Original scientific paper*

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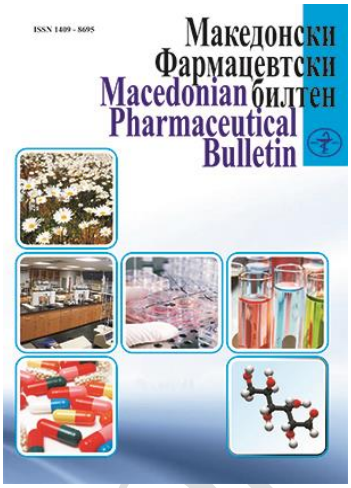
Accepted Manuscript



Title: Current treatment options and considerations for patients with relapsed/refractory diffuse large B cell lymphoma in North Macedonia

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DOI:
Received date: November 2021
Accepted date: December 2021
UDC:
Type of paper: Original scientific paper
Mac. Pharm. Bull. Vol. 67(2) 2021

Please cite this article as:

*Corresponding author e-mail: aleksandrapivkova@yahoo.com

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Current treatment options and considerations for patients with relapsed/refractory diffuse large B cell lymphoma in North Macedonia

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Abstract

Autologous stem cell transplantation (ASCT) is considered standard therapeutic approach for patients with relapsed and refractory (R/R) diffuse large B cell lymphoma (DLBCL) that are transplant eligible. For transplant ineligible patients there are few therapeutic options and novel targeted therapies and immunotherapy that are still in development. Treatment of such patients with poor prognosis is considered to be a challenge and there is constant need for new salvage treatment regimens. The aim of this study was to evaluate patients' characteristics and treatment strategies and considerations for diffuse large B cell lymphoma in our department, and to promote new therapeutic possibilities for R/R patients with NHL DLBCL. A total of 308 patients with NHL were treated at University Clinic for hematology from 2008 until 2020 and 49% (151) of patients with NHL DLBCL were included in this study. Survival analysis of all analyzed relapsed/refractory NHL patients revealed statistically significant better survival in patients with low risk IPI score, disease stage I/II and patients with age <60 years. R-CHOP was superior treatment as first line regimen and in the R/R patients, ASCT was statistically superior to other available second line treatment options. Overall survival in patients with DLBCL that achieved complete response after initial treatment was 80%. The incidence of disease relapse after initial treatment in the first 12 months was 18%.

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Overall survival in all treatment groups was 60% in the evaluated period of 2.5 years follow up. A total of 60% of patients with relapsed forms of NHL DLBCL were candidates for treatment with high-dose chemotherapy and ASCT. Other 40% patients were not candidates for ASCT. In conclusion we confirm the need for new treatment options for patients that relapse after ASCT and that are transplant ineligible. Patients and disease characteristics can be used to identify high-risk patients, classify once relapsed patients and define decision on further treatment.

Key words: relapsed and refractory lymphoma, autologous stem cell transplantation, survival, novel target therapy

Introduction

Diffuse large B cell lymphoma (NHL DLBCL) is the most common type of lymphoma representing 30% to 58% of cases. The incidence increases with age, DLBCL refers to 54% of NHL (non-Hodgkin lymphoma) cases in patients over 75 years of age (Tilly et al., 2015). A 5-year survival rates in the first-line setting can range from 60% to 70%, up to 50% of patients become refractory or relapse after treatment. Patients and disease characteristics can be used to identify high-risk patients, classify once relapsed patients and decision on treatment. (Cheson et al., 2014).

Autologous HSCT for transplant eligible patients is still considered the standard treatment for patients with refractory or relapsed (R/R) DLBCL and chemotherapy-sensitive disease (Shah et al., 2021). Transplant ineligible DLBCL patients and those who did not respond to first line immunochemotherapy treatment have poor prognosis and there is a need for effective salvage therapies (Harris et al., 2020). Novel targeted therapies and emerging immunotherapies (bispecific antibodies) are being developed for treatment of transplant-ineligible patients with R/R DLBCL (Palanca-Wessels et al., 2015). Adverse prognostic factors for auto-HSCT identified in prospective studies include early relapse within 12 months of induction therapy, prior exposure to rituximab, secondary age-adjusted international prognostic index (IPI), poor performance status, and involvement of two or more extranodal sites at relapse. Patients relapsing after auto-

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HSCT generally have a poor prognosis with limited therapeutic possibilities (Shadman et al., 2021).

The aim of this study was to evaluate patients' characteristics and treatment strategies and considerations for DLBCL in our department, and to promote new therapeutic possibilities for R/R patients with NHL DLBCL.

Patients and methods

Patients were diagnosed and treated at University Clinic for Hematology from January 2018 until June 2020. Patient data collection was provided according to medical treatment history. Statistical analysis was provided by Prism statistical software. Patients were evaluated on several variables: age, comorbidities, disease stage, IPI score, first line treatment regimen, relapse incidence, second line treatment regimen, overall survival, disease free survival and local policy.

Results

A total of 308 patients with NHL were treated at University Clinic for Hematology from 2008 until 2020 and 49% (151) of patients with HNL DLBCL were included in this study. Available statistical data was found in 129 (80%) of patients with NHL DLBCL. (Fig. 1).

Fig. 1

From the analyzed group of patients with NHL DLBCL according to gender distribution 75 (58%) were men and 54 (42%) were women. According to age distribution, 72 (56%) of NHL DLBCL patients were over 60 years of age. Mean age at diagnosis was 52 years (15 to 88) and medium SA (surface area) was 1.85m^2 (1.5 to 2.2), medium BMI (body mass index) was 32.3 (17.1 to 57.5). ECOG score was determined in 43% of the analyzed group of patients with NHL DLBCL. In 45% of patients ECOG score was rated 0 and 1. And 57% of patients had no medical history of ECOG score prior to initiation of first-line treatment. In 78% of patients with NHL DLBCL IPI index was 1

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and 2 before starting initial treatment and 20% of patients had IPI index 3 and 4. According to disease stage before treatment initiation 51% of patients with NHL DLBCL initially had advanced stage III and IV disease, 34% of patients had stage II and 6% had stage I. In 9% of patients there is no data on specific stage of the disease in the medical history. In the terms of first line treatment 78% of patients with NHL DLBCL were treated with R-CHOP as first-line treatment, 17% of patients received R + other chemotherapy, 3% of patients received only chemotherapy, 2% of patients received other chemotherapy regimens. (Fig. 2) After initial treatment 54% of patients achieved a complete response (CR) to first-line treatment confirmed by PET CT, 18% of patients had relapse or disease progression, 28% of the patients have an unconfirmed therapeutic response.

Fig. 2

A total of 60% (9) of patients with relapsed forms of NHL DLBCL were candidates for treatment with high-dose chemotherapy and ASCT. Other 40% (6) patients were not candidates for ASCT. Treatment of this patients with second line therapy is presented at Fig. 3. After high-dose of chemotherapy with R-ICE regimen, 4 patients had negative PET CT scan confirmed complete remission, 1 patient had residual disease before ASCT, 3 patients didn't complete second line chemotherapy due to lethal outcome and 1 patient was with disease progression on PET CT. Transplanted patients received conditioning according to BEAM regimen with median number of PBSC of $3.8x10^6$/kg CD34+cells (2.5 to 6.8).

Fig. 3

Patients that were not transplant eligible received second line chemotherapy and only one patient achieved complete response with negative PET CT.

Survival analysis of all analyzed relapsed/refractory NHL patients revealed statistically significant better survival in patients with low risk IPI score, disease stage I/II and patients with age <60 years (Fig. 4). R-CHOP was superior treatment as first line regimen and in the relapsed/refractory patients ASCT was statistically superior to other available second line treatment options in this study (Fig. 5). Overall survival in patients

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with NHL DLBCL that achieved complete response after initial treatment was 80%. The incidence of disease relapse after initial treatment in the first 12 months was 18%. Overall survival in all treatment groups was 60% in the evaluated period of 2.5 years follow up (Fig. 6).

Fig. 4

Fig. 5

Fig. 6

Discussion

Diffuse Large B-Cell lymphoma (DLBCL) is the most commonly diagnosed form of non-Hodgkin lymphoma (NHL) in adults and accounts for approximately one third of newly diagnosed lymphoma cases worldwide.

Accurate pretreatment evaluation and response assessment are critical to the optimal management of patients with lymphoma. With increasing knowledge of the disease, new prognostic factors, and a better understanding of tumor biology comes a need to update prior systems. The IPI takes into account five factors (age, stage, LDH, performance status, and number of extranodal sites involved). Patients within the low (IPI 0, 1), low-intermediate (IPI 2), high intermediate (IPI 3), and high-risk group (IPI 4, 5) can expect 3-year overall survival of 91.4%, 80.9%, 65.1%, and 59.0%, respectively, if treated with R-CHOP or one of its variants. In the analyzed group of patients 54% had initially advanced disease stage and in the terms of survival patients with higher IPI score had statistically significant worse survival than patients with lower IPI score.

Most patients receive an initial treatment with R-CHOP regimen. Cure rates are high but those patients who relapse, or do not respond to initial therapy, have a poor prognosis. (Walji and Assouline, 2020) In our group of patients RCHOP was initial treatment regimen for 78% of patients with success rate of 80% in achievement of complete response after first line treatment. The incidence of relapse at 2 years after initial treatment was 18%. Approximately 40% of patients with diffuse large B-cell lymphoma (DLBCL) will be refractory or relapse after first line therapy. Auto-HSCT is generally not recommended as part of first-line therapy in DLBCL although recent data on PET-

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guided auto-HSCT are promising. Transplanted patients in our center that had negative PET CT afted high dose chemotherapy had better survival after auto SCT. Adverse prognostic factors for auto-HSCT identified in prospective studies include early relapse within 12 months of induction therapy, prior exposure to R, secondary age-adjusted IPI, poor performance status, and involvement of two or more extranodal sites at relapse. The benefit of ASCT is greatest among patients with low IPI at relapse and with late relapses (occurring 1 year after first-line therapy) (Schmitz et al., 2019).

Although ASCT can cure a proportion of patients with R/R DLBCL, many patients cannot undergo this procedure because of toxicity or inadequate response to secondline chemotherapy. Before the development of chimeric antigen receptor T-cell (CAR-T) therapy, among patients with no response to chemo-immunotherapy or who relapse less than one year after ASCT, only 7% achieve CR following subsequent treatment. For patients that are not transplant eligible there are still limited therapeutic options, which was confirmed in the statistical analysis of our patients. The outcome of this patients is poor in our center and only one patient achieved complete response to second line therapy that was available at our hospital. So, there was a need for improvement of second line therapy in transplant ineligible patients which was defined in the local treatment strategy of DLBCL patients. (Fig. 7).

Fig. 7

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Резиме

Тековни опции за третман и размислувања за пациенти со релапсиран/рефракторен дифузен крупно-клеточен лимфом во Северна Македонија

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Клучни зборови: релапс и рефракторен лимфом, автологна трансплантација на матични клетки, преживување, нова целна терапија

Автологната трансплантација на матични клетки (АТМК) се смета за стандарден терапевтски пристап за пациенти со релапсен и рефракторен дифузен крупно-клеточен лимфом (ДЛБКЛ) кои се подобни за трансплантација. За пациентите кои не се подобни за трансплантација, постојат неколку терапевтски опции, нови насочени терапии и имунотерапија кои сè уште се во развој. Третманот на такви пациенти со лоша прогноза се смета за предизвик и постои постојана потреба од нови режими на третман. Целта на оваа студија беше да се проценат карактеристиките на пациентите и стратегиите за третман и да се промовираат нови терапевтски можности за релапсни-рефрактерни пациенти со ДЛБКЛ. Вкупно 308 пациенти со НХЛ биле третирани на Универзитетската клиника за хематологија од

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2008 до 2020 година и 49% (151) од пациентите со НХЛ ДЛБКЛ биле вклучени во оваа студија. Анализата на преживување на сите анализирани релапсирани/рефрактерни ДЛБКЛ пациенти откри статистички значајно подобро преживување кај пациенти со низок ризик ИПИ резултат, фаза I/II на болеста и пациенти на возраст <60 години. R-CHOP беше супериорен третман како режим на прва линија и кај пациентите со релапсни рефрактерни форми на болест, АТМК беше статистички супериорен тераписки пристап во однос на другите достапни опции за третман од втора линија. Целосното преживување кај пациенти со ДЛБКЛ кои постигнале целосен одговор по почетниот третман беше 80%. Инциденцата на релапс на болеста по почетниот третман во првите 12 месеци беше 18%. Целосното преживување во сите групи на третман беше 60% во проценетиот период од 2,5 години следење. Вкупно 60% од пациентите со релапсирани форми на ДЛБКЛ биле кандидати за третман со високи дози на хемотерапија и АТМК. Останатите 40% пациенти не беа кандидати за АТМК. Како заклучок, ја потврдуваме потребата од нови опции за третман за пациенти кои релапсираат по АТМК и не се подобни за трансплантација. Пациентите и карактеристиките на болеста може да се користат за да се идентификуваат високоризичните пациенти, да се класифицираат пациентите со релапс на болест и да се дефинира одлука за понатамошен третман.

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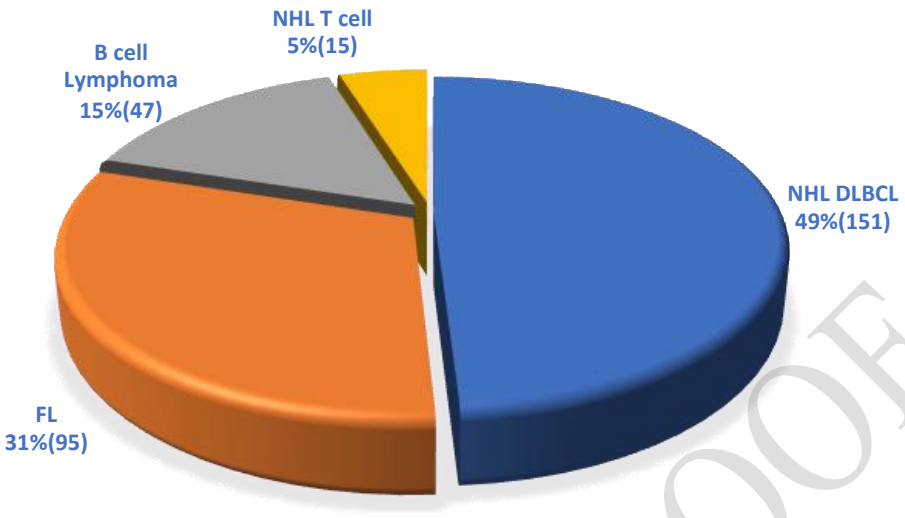

FL- follicular lymphoma, NHL DLBCL- diffuse large B cell non Hodgkin lymphoma

Fig. 1. NHL patients treated at University Clinic for Hematology in the period from January 2018 till June 2020.

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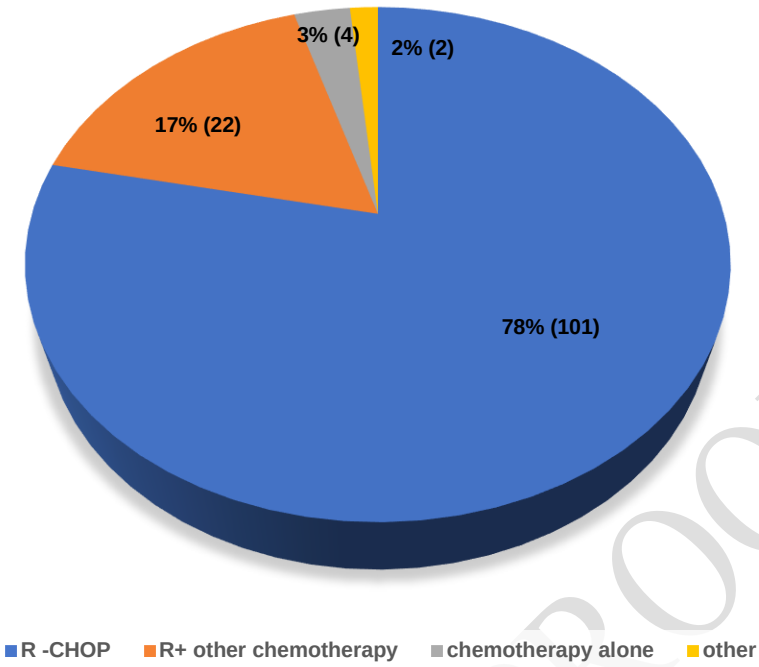

Fig. 2. First line treatment of NHL patients treated at University Clinic for Hematology in the period from January 2018 till June 2020.

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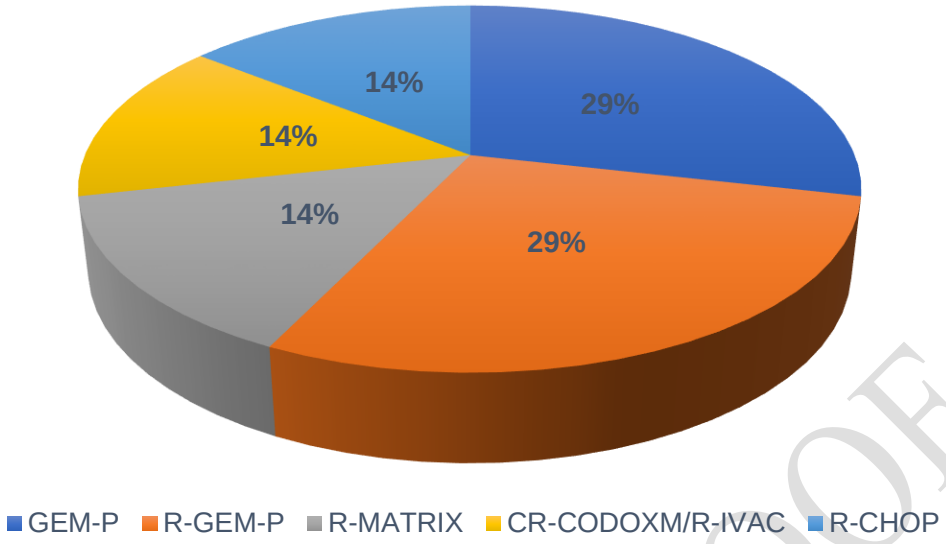

Fig. 3. Second line treatment of transplant ineligible NHL patients treated at University Clinic for Hematology in the period from January 2018 till June 2020.

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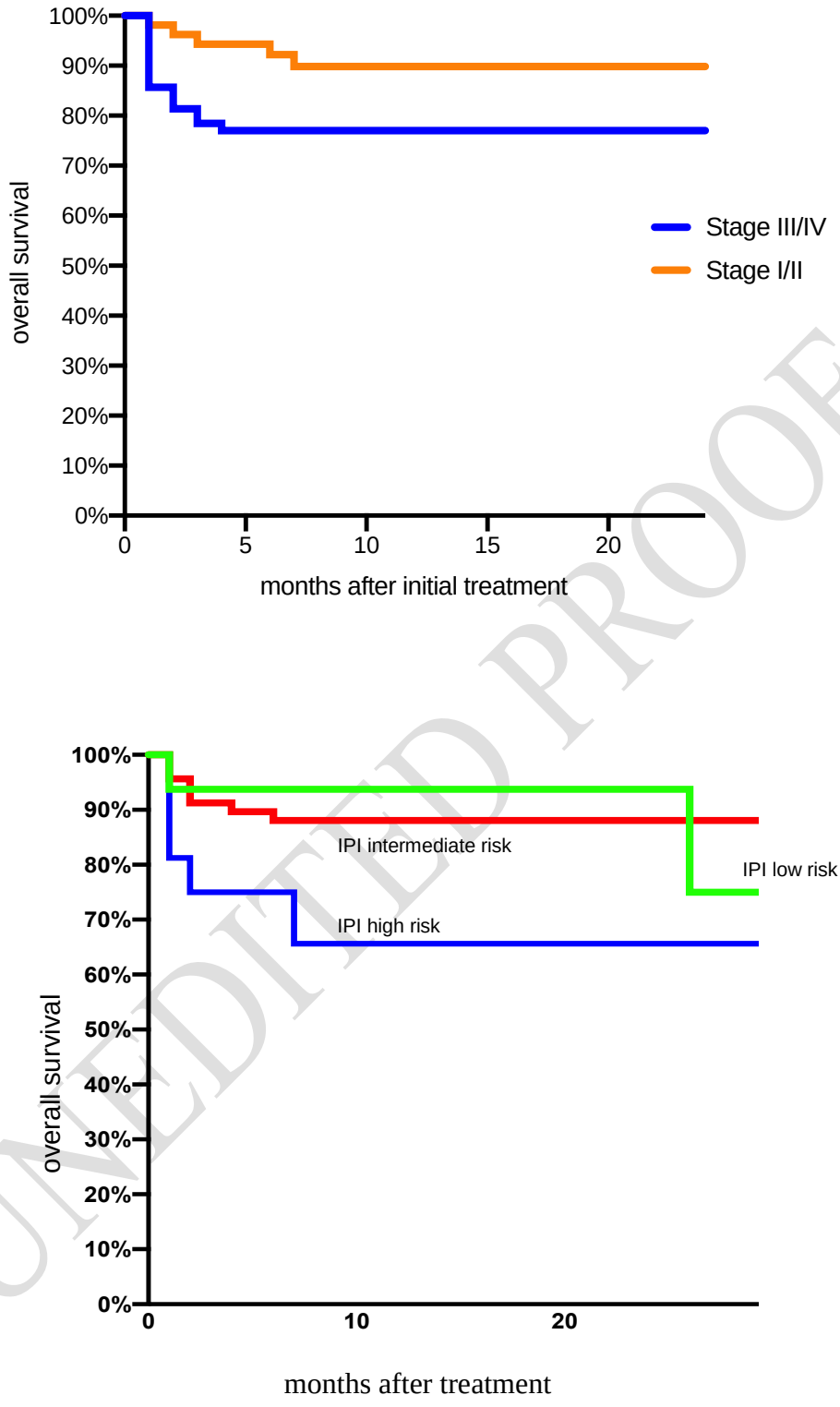

Fig. 4. OS of patients according to disease stage at diagnosis and IPI score (*p=0.02*).

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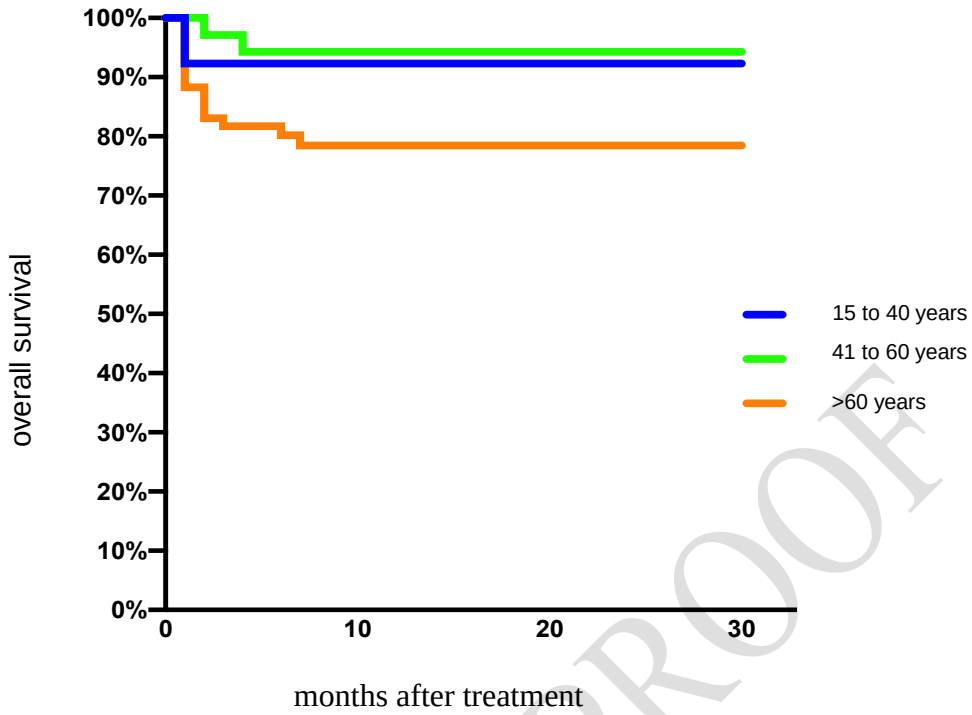

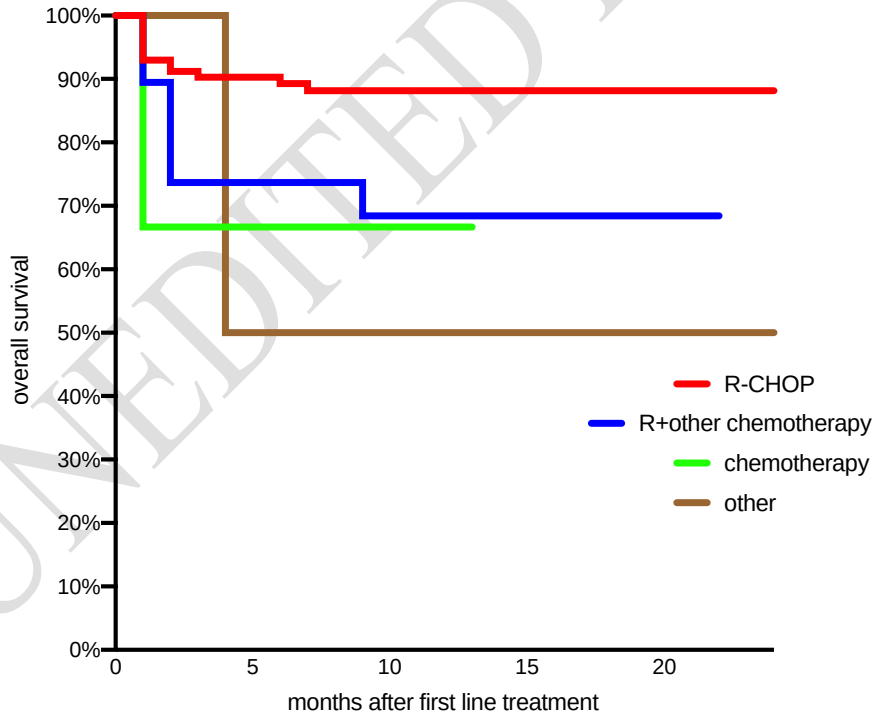

Fig. 5. OS of patients according to age (*p=0.02*) and type of first line treatment (*p=0.0165*).

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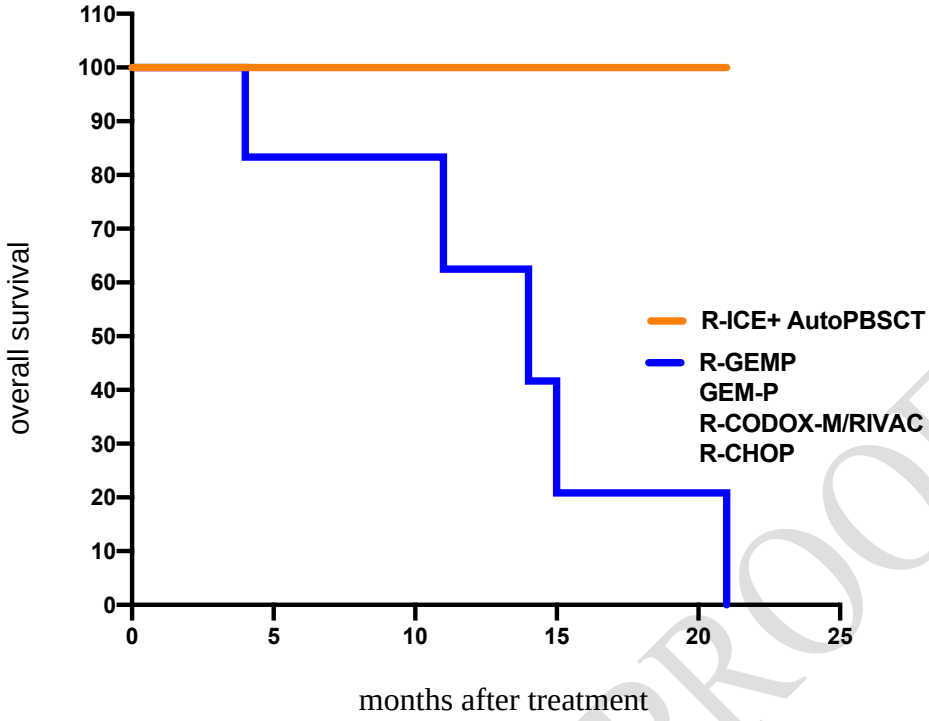

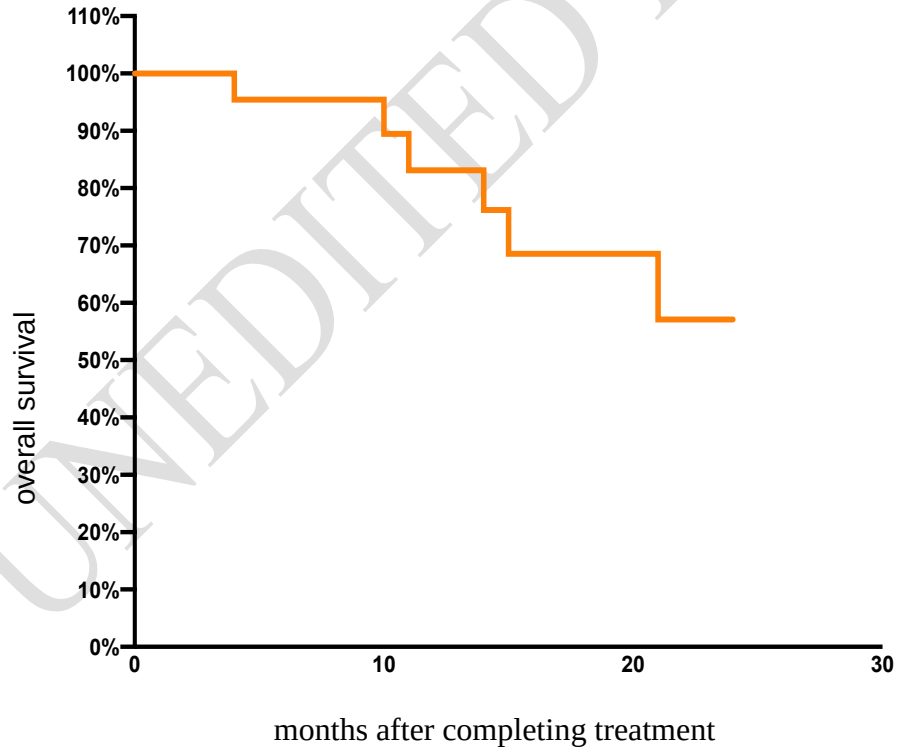

Fig. 6. OS of relapsed/refractory NHL patients after secondline treatment.

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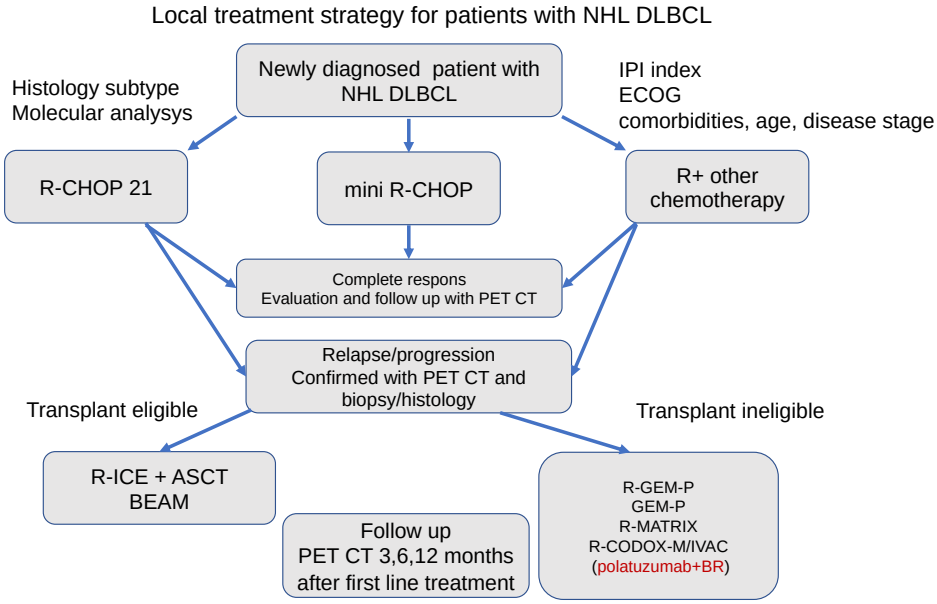

Fig. 7. Local treatment strategy for patients with NHL DLBCL.

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