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MILESTONES IN HEMATOLOGY AND ONCOLOGY: FROM FATAL TO CURABLE DISEASE

Progress in the management of patients with Hodgkin's lymphoma in the Republic of North Macedonia: experience from 40 years of population-based study

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ABSTRACT

Background: The comprehensive management of patients with Hodgkin's lymphoma (HL) is a success story in contemporary oncology. Over the past decades, the survival rate of patients with HL has significantly improved. The objective of this analysis is to evaluate and document the progress in the management of Hodgkin's lymphoma in patients in our country, reflected in their vital statistics, over time periods defined by the respective standard of treatment.

Material and methods: The present study is designed as a retrospective-prospective study. We analyzed different modalities of treatment and compared 5 and 10-year overall survival rates in a total of 588 Hodgkin's lymphoma patients treated at the University Clinic for Hematology in Skopje during two consecutive time periods, before 2000 and after 2000. The entire observation period is from 1980 to 2020. All patients are above the age of 14, with a documented histopathological diagnosis of Hodgkin's lymphoma and with evaluable medical documentation, including clinical and laboratory data on their initial condition, the administered therapy, as well as the clinical follow-up of the patients.

Results: The basic clinical features of the analyzed population across the two periods correlate with those reported in the relevant medical literature, with only slight deviations. Ten-year overall survival rates improved by 31.7% through the two calendar periods. During the last two decades of the previous century (1980-2000) the initial treatment options were COPP and COPP-like regimens for the vast majority of patients (94.7%), leading to disease remission in 80% of them. After 2000, 95.8% of de novo diagnosed patients have been treated with ABVD chemotherapy as a frontline choice and the complete response rate is 88.4%. We confirmed the superiority of ABVD in terms of efficacy, improved tumor and disease control, as well as its long-term clinical outcome. While in the past we had very limited options for relapsed/refractory HL patients, the analysis of the results of HL patients treated with various therapeutic approaches in the latter period, defines BEACOPP as the preferred choice. High-dose chemotherapy, followed by autologous hematopoietic stem cell graft, as a strategy for our R/R patients in the timeframe after 2000, ensures a 5-year overall survival for 51% of them, whereas 45% of the patients survive more than 10 years.

Conclusion: This analysis from our Hodgkin's lymphoma database illustrates that there has been tremendous improvement in the long-term survival rates since the turn of this century. At our institution we strive to implement positive trends in practice, as suggested by relevant guidelines, regarding the evolution and progress in the diagnostic workup, treatment, and the overall management of patients with Hodgkin's disease. The objective would be to secure favorable vital statistics for our patient population, now reaching 83.5% at 10 years, which closely correlates with the data of more developed countries and centers. In future clinical trials we will also evaluate the efficacy of brentuximab-vedotin and new PD-1 blocking antibodies.

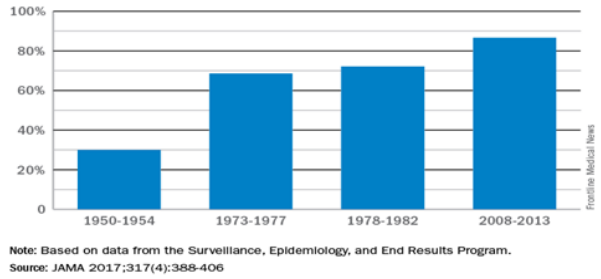
Keywords: Hodgkin's lymphoma, overall survival, treatment, progress

INTRODUCTION

Hodgkin's lymphoma is a malignant lymphoproliferative disorder, a symbol of a therapeutic triumph over malignant neoplasms. It represents the first cancer successfully treated with both chemo- and radiotherapy.

It is mainly attributable to the increased treatment quality that the survival of patients with Hodgkin's lymphoma has tripled over the past six decades. In the early 1950's, the 5-year overall survival for these patients was limited to around 30%, whereas in the early years of the new millennium it has increased to an impressive 86.6% (Figure 1.) [1].

Figure 1. *Survival rates from 1950 until 2013 have increased almost threefold.*



The progressive improvement in survival rates is also due to advances in the understanding of the disease biology, the development of sophisticated visualization methods, establishing risk factors and defining prognostic categories, the development of new classes of drugs and, with it, subsequent lines of therapies, managing these patients with a multidisciplinary and contemporary medical approach. The evolution and advances in supportive treatment, the precise and timely recognition of poor treatment outcomes and failures, as well as the implementation of tailored therapy in accordance with the assessment of the condition of the patient and the disease extent have all contributed to this threefold improvement. [2-6]

In general, four different effective treatment modalities are utilized: combination induction chemotherapy, radiotherapy, salvage chemotherapy, and high dose chemotherapy followed by autologous hematopoietic stem cell transplant. Choosing a treatment plan requires considering several factors, such as the histology of the disease, its clinical stage, whether the patient is newly diagnosed, or with refractory or relapsed disease, patient's age, possible existence of comorbidities, the performance status of the patient, and other well defined and characterized risk factors.

The pioneering induction combination MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) chemotherapy was composed and administered by DeVita et al. [7] According to reports from the National Cancer Institute, in one series of 188 treated patients with advanced stage HD, 54% remained in long-term remission following MOPP chemotherapy. [8] However, it took a considerable amount of time to acknowledge that this regimen is associated with a considerable rate of myelosuppression and infertility, as well as with an increased risk of developing secondary myelodysplasia and acute leukemia. [9, 10] Most of our patients treated for HL before 2000 received COPP induction chemotherapy (a derivative of MOPP, where nitrogen mustard is substituted with cyclophosphamide). [11]

The ABVD combination chemotherapy regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) was constructed and introduced more than 40 years ago by Bonadonna. It is still considered to be the treatment standard for HL, achieving cure in 70-80% of the patients [12]. This regimen has been adopted as a gold treatment standard in the management of HL patients at our institution since 2000. [13]

The ABVD regimen does not end the search for innovative, more successful treatment options. At the start of the new millennium, the German Hodgkin Study Group (GHSG) published their initial encouraging results in treating HL patients with the newly assembled and even more aggressive BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). [14] In subsequent studies, BEACOPP was established as a very efficient regimen, achieving a high overall survival rate and complete remissions, as well as durable responses in patients with unfavorable, advanced stage HD. The regimen has accomplished impressive, progression-free survival rates in several head-to-head comparative analyses against the ABVD scheme. [15-20] However, the incidence of immediate hematological adverse side effects and complications, infective episodes and disorders of the reproductive system and function, are systematically more frequently reported in patients treated with the BEACOPP regimen. At our institution, we have introduced this aggressive

scheme gradually, with caution and meticulous monitoring. Our first experiences were obtained from administering this schedule in patients failing standard induction chemotherapy. In the years after, we gradually increased the number of initially treated patients receiving the BEACOPP scheme as induction chemotherapy. This was done mostly among patients with advanced stage disease and with initial poor risk assessment. We have yet to perform a comparative evaluation and statistical analysis of the effects achieved in patients treated with each of the regimens at disease presentation, since the cohorts are still quite uneven in terms of numbers.

Historically, radiotherapy is extremely relevant with regards to the treatment of HL patients. Decades ago it represented the single curative option for this disease, and it was complementary in all limited stage HL patients treated in the MOPP regimen era, administered over a rather broad field and with large radiation doses delivered. The most frequently used model was the mantle field irradiation, encompassing the neck, axillary region and the mediastinum for supradiaphragmal presentation, and the inverted Y-field irradiation of the paraaortal and both inguinal areas for the infradiaphragmal type of HL presentation.

Modern guidelines recommend only the involved field (not area, region, or site), more precisely involved node irradiation, enabled by contemporary developments in radiotherapy, delivering a significantly reduced dose of radiation. Radiotherapy maintained its substantial significance in primary chemorefractory disease, when it is administered as an adjuvant treatment over a residual tumor mass.

In spite of the improvements in the management of HL patients, in 5-10% the obtained response is not satisfactory, or the disease progresses under treatment or within a month following treatment completion (primary refractory disease). In 10-30% of patients, disease relapse occurs even if initially a complete response was obtained. The management of patients with relapsed/refractory (R/R) disease is especially demanding and challenging. The single potentially curative approach for such patients is high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HDCT+AutoSCT). [21, 22] This approach has shown encouraging results in patients with R/R HL, resulting in 5-year progression free overall survival for 30-65% of the patients. [23–25] The launch of the Transplant Unit in our Clinic in 2000 and the starting of bone marrow and subsequently of hematopoietic stem cell transplants as treatment options has become the step forward in the line of possibilities for managing HL patients.

For the patients in which the disease progresses in the course of, or immediately after the end of treatment administration, as well as for those who experience a relapse within one year following high dose chemotherapy followed by autologous hematopoietic stem cell transplant, the prognosis is considerably poorer, resulting in a mean overall survival duration of 1.2 years. [26] There was no evident medical treatment option for such patients until the 2010s, when two innovative and highly efficient strategies for this high risk patient population were introduced: the antibody-drug conjugate brentuximab vedotine and antibodies blocking the immune control sites (immune checkpoint inhibitors), nivolumab and pembrolizumab. [27–34]. An option to be considered is also the allogeneic stem cell transplant (AlloSCT), providing long-term remissions in 20-59% of patients. Unfortunately this comes at the cost of high transplant related mortality, [35–37] an undesired outcome which has been successfully moderated more recently. During the past five years we have engaged in administering innovative treatment options, beginning with younger overtreated patients, manifesting refractoriness to multiple lines of therapy. The observation period is still quite short, therefore requiring more time in order to assess our own efficacy results and derive our initial conclusions.

One of the fundamental goals of this study was to assess the evolution and progress in the management of HL patients treated at the University Clinic for hematology in Skopje in two different calendar periods, utilizing a variety of statistical operations. Around 2000, the Clinic established standards regarding the scope of diagnostic procedures, risk factor assessment, initial standard treatment options for the disease, interventional and supportive treatment for disease or treatment complications, respecting guidelines and recommendations published by respected and renowned peer experts and institutions.

The continuous and permanent storage, and hence availability, of comprehensive individual data for every single patient (as we are the single adult hematology institution in the country), as well as repeated analyses, presentations and publications addressing the management of our

patients before 2000, enables us to compare the progress on all management levels, and this allows us also to assess whether this has been adequately and positively reproduced in true improvements of vital statistic parameters and the quality of life for patients.

MATERIALS AND METHODS

For the aims of this study, data have been analyzed from the hospital records of patients treated at the University Clinic for Hematology in Skopje, thus classifying the study as retrospective-prospective. The analysis includes 588 patients with a diagnosis of HL, evaluated and treated at the Clinic between 1980 and 2015, with continuous observations until 2018. The clinical assessment of our HL patients followed an established diagnostic algorithm, consisting of clinical presentation data, laboratory results, data received from visualization methods performed, as well as the results of pathohistological and immunohistochemical examinations performed on biopsy specimens. Clinically relevant variables included demographics (age, gender, etc.), histological type, extent of the disease labeled as clinical stage, and presence or absence of characteristic symptoms (type B or A). The year of diagnosis was used as the determinant for inclusion of the patient in one or the other group within the analysis.

The designated goal was to detect the eventual progress of survival in patients with Hodgkin's lymphoma, based on the difference in treatment over time.

In order to reveal and document eventual improvements in survival over time the cohort was divided into two timeframes of monitoring, 1980-2000 and 2005-2015, and the overall survival rates were calculated by the timeframes of observation. Overall survival was the primary endpoint of our analysis, defined as the interval from the date of diagnosis to the date of last observation or death from any cause.

Analyses of overall survival are a key component in monitoring progress against cancer. For these reasons, our analyses were initially designed towards estimations of overall survival, as that is the most commonly reported parameter of significance for vital statistics by cancer registries, and it can be widely recognized and conclusively interpreted by a broad scientific audience in a straightforward manner. Additional outcome evaluations were directed towards the comparative categorization of the quality of response (according to Cotswold's criteria) under diverse treatment approaches.

The estimates of overall survival (OS), as well as other vital statistics deliverables in the different calendar periods were calculated using the Kaplan–Meier method.

The data were analyzed using the Statistical Analysis Program, SPSS 17.0.

RESULTS

The number of patients in each of the calendar subgroups is comparable. Stratified analyses by time period allows comprehension of the overall picture, as well as outlining the differences in distribution, regarding the clinical characteristics of HL patients (Table 1).

The baseline characteristics of the two groups did not differ significantly. One exception is the comparably high frequency of the LP histology subtype before 2000, which could be explained by the changes in classification occurring later. Namely, the rare variant, nodular lymphocyte rich (predominance) type of HL, is classified as a separate entity in the WHO classification of Hodgkin's lymphoma of 2008. Also, it can be noted that, in total, the main distinguishing characteristic accounted for by the pathologists was the quantitative presence of lymphocytes, consigning more than half of the diagnosed HL cases to the extreme subtypes. Clearer description of the histology, as well as inclusion of immunohistochemical characterization contributed to changes in the diagnosis of subtypes, consistent with findings in more experienced centers, thus subsequently resulting in the nodular sclerosis subtype being the most frequently diagnosed form of HL. Regarding the clinical presentation, the diagnosis of a limited stage HL was more frequent in the period following 2000, for which improvements in visualization methods could be considered as the underlying reason.

Table 1. *Patients' characteristics in the two analyzed timeframes*

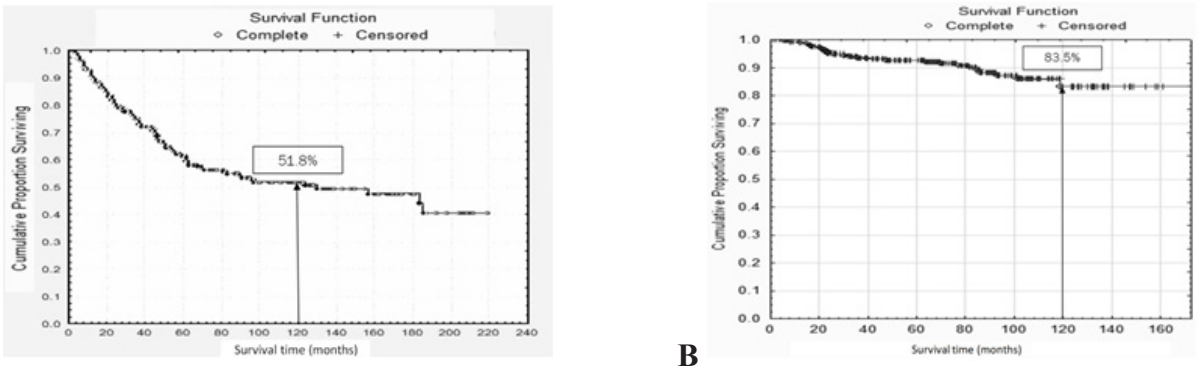
Characteristic		Calendar period No (%)	
		1980-2000	2005-2015
Gender	Male	198 (65.8%)	152 (53%)
	Female	103 (34.2%)	135 (47%)
Age	Median age, years	38.0	36.6
	<35 years	148 (49.1%)	152 (52.9%)
	>35 years	153 (50.9%)	135 (47.1%)
Pathology Subtype	Nodular sclerosis	57 (18.9%)	131 (45.6%)
	Mixed cellularity	54 (17.9%)	90 (31.4%)
	Lymphocyte depletion	72 (23.9%)	10 (3.5%)
	Lymphocyte predominant	104 (34.6%)	26 (9.1%)
	Nodular lymphocyte predominant	/	17 (5.9%)
	Non differentiated	14(4.7%)	13 (4.5%)
Clinical Stage	I	37 (12.3%)	49 (17%)
	II	80 (26.6%)	95 (33.1%)
	III	118 (39.2%)	64 (22.3%)
	IV	66 (21.9%)	74 (25.8%)
	Undefined	/	5 (1.8%)
Characteristic Symptoms	Yes (B type)	200 (66.4%)	62.7%
	No (A type)	101 (33.6%)	37.3%
International Prognostic Index	≤3	219 (72.3%)	247 (86.1%)
	≥4	82 (27.2%)	40 (13.9%)

In regards to the administered chemotherapy regimen, the majority of patients (94.7%), in the analyzed subgroup before 2000 received COPP (a derivative of MOPP, a MOPP-like regimen), while following 2000, the patients initially received ABVD as a therapy of choice (95.8%), whereas COPP fell to only 2.4%. Up until time of writing, ABVD has remained our first choice for first line treatment of HL patients, allowing us to evaluate efficacy advantages in this analysis. The overall response rate, encompassing all patients who reach a stage of remission lasting longer than six months, is registered at 88.1% of the treated patients, or in 252 of the 287 total. Nevertheless, 9.8% of the patients remain primarily refractory to this type of treatment. Among the patients initially achieving a CR, one or subsequent relapses have been documented in 16%, or 46 patients. Fatal outcome during the initial treatment is registered in 2.1% of the patients.

Being a constitutive component of the treatment modality for a defined disease profile, 27.5% of patients diagnosed after 2000 underwent adjuvant radiotherapy as well, being entirely of the involved field (IFRT) type. Radiotherapy had been employed in 30.2% of the patients treated prior to 2000, but it was mostly extensive, with only 40.6% of patients receiving IFRT.

Comparative vital statistics analyses reveal a remarkable improvement in overall survival (OS) in favor of the more recently diagnosed patients. For the subgroup treated between 1980 and 2000 the 5-yr and 10-yr OS was 61.3% and 51.8%, while in the subgroup treated in this century the rates increased to 94% and 83.5% respectively, which is graphically illustrated in Figure 2.

Figure 2. *Overall survival for patients with Hodgkin's lymphoma in the two calendar periods. (A) 1980-2000, (B) 2005-2015*

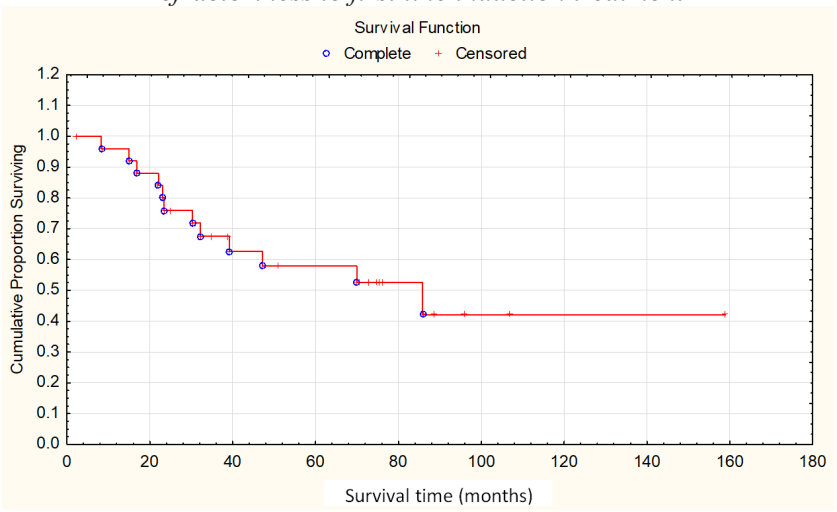


By contrast, figure 2A reflects the survival experience of patients diagnosed in 1980-2000.

The OS curves of the patients with HL diagnosed in the 2 periods showed remarkable improvement in their OS over time.

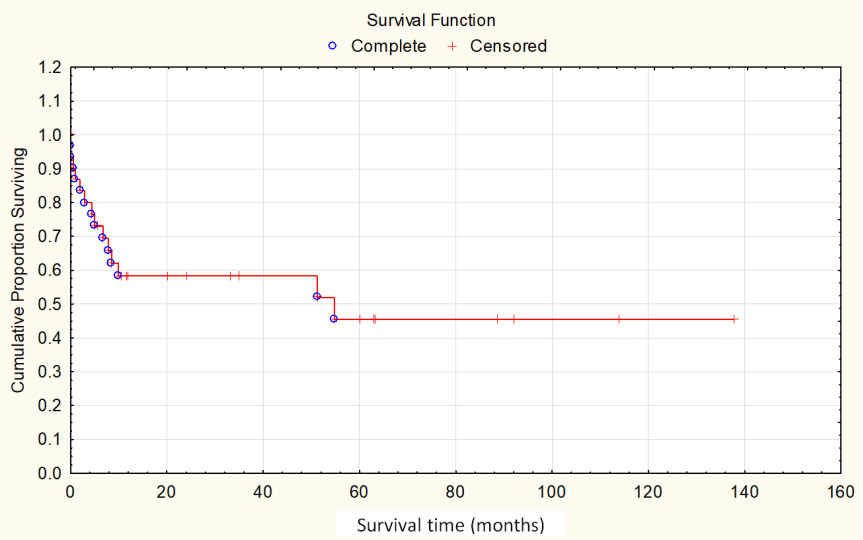
Should the patient not have achieved a state of complete remission or should she/he have experienced the first disease relapse, the majority of them (36.1%) received BEACOPP chemotherapy as a second line choice. Regardless of the second line treatment administered, relapsed/refractory patients achieved an overall response rate, i.e. state of remission, in 59.7%, whereas if analyzed by treatment type, BEACOPP induced remission in 65.4% of these patients. The estimated overall survival probability for this subset of patients is portrayed in Figure 3.

Figure 3. *Analysis of overall survival of HL patients manifesting refractoriness to first line induction treatment*



Autologous stem cell transplant was performed in 31 patients, at an average age of 31.8 ±11.4 years, ranging from 16 to 56 years. In 38.7% of the transplanted 31 patients, a state of achieved remission resulted from the procedure and it has been sustainable during the entire period of observation. Nevertheless, 58.1% of these patients experienced a disease relapse, and one patient had a fatal outcome related to the transplant procedure. Regarding sustained responses, estimated PFS in patients following the HDCT+AutoSCT procedure is 48% at the point of 60 months of observation, while 50% of the patients reach 52.3 months without disease progression (Figure 4).

Figure 4. *PFS in patients receiving salvage high dose chemotherapy followed by autologous hematopoietic stem cell transplant*



DISCUSSION

During the past few decades we have witnessed remarkable progress in several hematology segments, but also in oncology in general. The development of innovative, highly efficient chemotherapy combinations, optimization of radiotherapy, in terms of dose administered, but also in terms of the meticulous defining of field margins by using advanced technologies, the introduction of various modalities of immunotherapies, as well as wide implementation of stem cell transplant options, have contributed to obtaining the primary goals of treatment. Innovative visualization methods, especially PET scans in combination with CAT, have enabled greater precision in diagnosing neoplastic changes, i.e. unambiguous staging definitions, but also the intermediate and final evaluation of treatment results, thus influencing eventual changes in therapeutic choices and approaches. Individual treatment choices, widely referred to as tailored therapy, have been enabled by establishing prognostic factor systems, based on which risk assessment is performed. Supportive capabilities have been significantly expanded, especially in the segment of post-therapeutic myelosuppression, infectious, and other types of treatment complications. These focal points have markedly contributed to the cure of the majority of patients with HL (75-90%). Therefore, the progress cannot be attributed solely to the development of new drugs, but mostly due to the development of a palette of treatment options, among which the clinicians can choose and administer the most adequate one(s), in accordance with the assessment of risk category and initial presentation and propagation of the disease.

The evolving innovations and the progress in assessment of a comprehensive and definite diagnosis, the variety of treatment modalities and options, the ability to control the disease, the possibilities for a successful treatment and successfully managing the HL patients in general, have been scrupulously pursued and practiced at our Clinic. Initially, we had expressed hope, but from this perspective we can now confirm that the desired effects, reflected in improvements of the vital statistics of the HL patients, have become a very tangible reality in the more recent timeframe.

Comparative statistical analysis of the cohorts of patients treated in the two different timeframes reveal that:

• in patients treated before 2000, the estimated 5-year OS probability was reached by 61.3% of patients, while their 10-year survival rates plateaued at 51.8%;

• in the cohort treated after 2000, 5-year OS was achieved by 94.0% of the patients, while their 10-year OS is estimated for 83.5% of the patients;

• the almost 33% improvement in margin, a notably significant increase in OS probability, is undoubtedly the "pièce de résistance" of this study, revealing a clearly and scientifically derived conclusion and the confirmation of the

progress achieved at our institution as well, regarding the treatment and overall management of the patients with HL (Figure 2.).

• Following the introduction of the ABVD regimen in hematology as a superior treatment option, we started using it at our site as a second line option, i.e. for patients who failed the initial COPP(-like) treatment. Since the mid-1990s, we started administering ABVD as a first line choice, but only in a relatively small proportion of patients, alongside the "hybrid" COPP/ABVD combination. Finally, in the beginning of this millennium, ABVD has become the standard first line treatment option for all of our newly diagnosed HL patients. Therefore, a comparative statistical analysis of patients treated with the different induction modalities, before and after 2000, emerged as a requirement.

Administered as induction therapy in our patients treated in the 2005-2015 period, the ABVD regimen induces complete responses at a rate of 88.4%, a result equal to those published in relevant medical literature by peer experts and centers.

Nevertheless, although the desired positive response (CR) to treatment was achieved with the initial therapy approach, 16% of the patients experienced a relapse, and 9.8% of the patients remained refractory to initial treatment.

The latter groups of refractory and/or relapsing patients pose an extraordinary focus of interest, as their further management represents a continuous challenge. In the not so distant past, we had no promising solutions for refractory HL patients, and the estimated survival rates for patients with a state of remission lasting 12 months or less were quite discouraging (only 5% surviving longer than 80 months). The evolution and advances in the successful management is very evident in relapsed/refractory (R/R) HL patients at our institution, achieving overall survival rates following first relapse or when treated for refractoriness, by administering second line therapies, of 61% at 5 years, and 59% at 10 years. This result is mainly attributed to the efficacy and potency of the BEACOPP regimen when administered to high risk HL patients, as well as to high dose chemotherapy followed by an autologous stem cell transplant, a method offering added curative potential for R/R HL patients following multiagent conventional therapy. Although HDCT and autotransplant has been used as an approach in HL patients since the late 1980s, in the past few decades it has been established as a standard of treatment in guidelines regarding R/R HL patients. If treated only by conventional chemotherapy with escalated doses, these patients have a significantly feeble prognosis and outcome. There are many publications which report having achieved sustained remissions in a significant proportion of patients with R/R HL, where the disease is otherwise labeled as incurable with conventional treatment approaches. Our transplant unit commenced activities in 2000, initially introducing the procedure of bone marrow transplants as a potential treatment option. This represented a huge qualitative step forward in the management of HL patients, among others. Out of the total number of transplanted patients in our unit, 20% are performed in HL patients. Among patients treated with this approach, sustained responses throughout the entire observation period are registered in 38.7% of them. The results and rates emerging from our analysis, regarding the overall survival rate estimates and progression free survival estimates, for patients that underwent HDCT+AutoSCT, are very comparable with the data from the EBMT registries. The transplant related mortality rate, i.e. the mortality rate not caused by the disease itself, is 3.2% for these patients. Despite the relatively small size of the analyzed patient subgroup in our study, our results support and validate the premise that HDCT+AutoSCT is able to induce durable disease control and secure a significantly improved prognosis for patients with R/R HL. The analysis of the treatment approach using innovative immunotherapy for our R/R HL patients will require further comprehensive analyzing following an adequate perspective in terms of duration.

Addressing issues in a significant number of patients, and having a substantial duration of follow-up, our study provides several noteworthy conclusions. It is well documented that our patients treated after 2000 have a statistically significant increase in 10-year estimate rates, a result that accounts for the following rationales:

• the ABVD regimen has been established as the induction treatment standard, since it has a proven superiority compared to COPP and COPP-like regimens, which were the frontline choices in earlier decades; ABVD produces superb tumor control, increasing the CR rate and improves the vital statics and prognosis in HL patients by a substantial margin;

• there is a lower incidence of treatment complications, manifestations of toxicity and therapy related adverse effects with ABVD in general; for many of such complications the first two decades of this century have supplied us with an armamentarium of wide variety;

• in the past we did not have a beneficial solution for HL patients that entered the category of refractory/relapsed disease; the new millennium provided a sizeable variety of opportunities: more aggressive chemotherapeutic regimens, high dose chemotherapy followed by AutoSCT, immunotherapy, etc.;

• progress and technological advances have led to the development of more sophisticated techniques for the visualization of neoplastic changes; availability of modern diagnostics resulted in a more rapid and comprehensive assessment and staging of the disease; accumulated knowledge and experience led to the construction of prognostic factor systems, on the basis of which risk categories were defined; hence, in more recent decades, assessment of advanced disease stages (III and IV), as well as of high risk scores (poor prognostic factors) in our analyzed HL patient population, have declined substantially: advanced stages in the 1980-2000 era were diagnosed in 61.1% of HL patients, as opposed to 48.1% in the 2005-2015 period; respectively high IPS scores (≥4) were defined in 27.2%, as opposed to 13.9% of patients; hence, earlier diagnosis in the more recent timeframe enabled us to deal with a higher proportion of patients with disease in a limited (localized) stage, at the same time being classified as low (favorable) risk category.

In general, the challenge to define arguments that would explain the advances in vital statistics and prognosis, would ultimately finish with two topics: early assessment of diagnosis and propagation, and the more favored advances and innovations in treatment. Nevertheless, we would like to offer a more comprehensive insight into our findings.

The earlier constructed chemotherapy regimens did not have a pharmaceutical industry developed as much as it is now, both in the sense of technologies as well as in knowledge and research capacity. It was only normal that we were experiencing severe adverse effects, such as myelosuppression with all of its consequences, with none, or very limited tools for dealing with them and controlling them. Today we have a wide palette of supportive care, the means of alleviating undesired side effects, and an array of possibilities in substitution therapy, i.e. blood components.

We have set standards for monitoring HL patients, knowing that adverse effects can be early, but also quite delayed and very debilitating. Both early and late complications additionally increase the morbidity and mortality rates in HL survivors. Continuous monitoring enables timely reactions to manifested changes in the general health condition of a patient, and securing options for successful management.

Having the possibilities for immediate and accurate visualization of all affected sites, is a huge contribution to the rapid assessment of the extent of the disease. Furthermore, we can now also monitor the patients during therapy and eventually make decisions regarding length, or possibly switch of treatment, based on those findings, more generally labeled as tailoring therapy. The most we had available to us in the previous century was CAT, and occasionally MRI. We are delighted to state that in the 2010s we have almost completely switched to PET scan imaging, appreciating the possibility to diagnose not only anatomical alterations, but also functional activity of the neoplasm. It has been set as a standard of care that each patient undergoes an initial, at least one intermediary, and one final PET-CT scan procedure, as well as further follow-up examinations if necessary. This management strategy also enables us to adhere strictly to treatment guidelines, minimizing both the possibility for undertreatment, as well as overtreatment according to the risk category, but also to change the treatment plan if the findings impose such an action.

CONCLUSION

Once only treatable with radiotherapy, the management of Hodgkin's lymphoma became the pride of hematologists, a triumph of science, medicine, and humanity in general over an otherwise fatal disease. Today it can be defined, at least, as a highly treatable and curable malignant neoplasm. Having been engaged in this specific segment of hematology during several decades and providing new generations of doctors to continue close monitoring of these patients, we are

grateful and content because synchronizing and harmonizing our management strategies with peer guidelines and recommendations has been the prerequisite for experiencing a comparable degree of satisfaction regarding the outcomes in our patients. Some bold prophecies which were unthinkable, or remained unspoken several decades ago, are reality now, creating an aura of a magician around us: we can cure malignancies.

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Appendix 1

LIST OF ABBREVIATIONS

HL: Hodgkin's lymphoma

COPP: cyclophosphamide, oncovin (vincristine), procarbazine, prednisolone

ABVD: adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine

BEACOPP: bleomycin, etoposide, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), procarbazine, prednisolone

PD: programmed death (protein)

MOPP: mustargen (nitrogen mustard), oncovin (vincristine), procarbazine, prednisolone

GHSG: German Hodgkin Study Group

R/R: relapsed/refractory (disease)

HDCT: high-dose chemotherapy

AutoSCT: autologous stem cell transplant

AlloSCT: allogeneic stem cell transplant

OS: overall survival

LP: lymphocyte predominant (HL type)

CR: complete remission

IFRT: involved field radiotherapy

PFS: progression free survival

PET: positron emission tomography

CAT: computerized axial tomography

EBMT: European (Society) for Blood and Marrow Transplantation

MRI: magnetic resonance imaging

IPS: International Prognostic System

Резиме

ПРЕСВРТНИЦИ ВО ХЕМАТОЛОГИЈАТА И ВО ОНКОЛОГИЈАТА: ОД ФАТАЛНА ДО ИЗЛЕЧИВА БОЛЕСТ

Напредоци во згрижувањето на пациентите со Хоџкинов лимфом во Република Северна Македонија: искуства од 40-годишна популациона студија

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Вовед: Севкупното згрижување на пациентите со Хоџкинов лимфом (ХЛ) е успешна приказна во современата онкологија. Низ изминатите децении преживувањето на пациентите со ХЛ е значајно подобрено. Целта на оваа студија е да се процени и да се документира напредокот во згрижувањето на пациентите со ХЛ во нашата земја, низ промените во нивната витална статистика во различни временски периоди дефинирани според тогашниот тераписки стандард.

Материјал и методи: Ова е студија од ретроспективно-проспективен тип. Ги анализиравме различните тераписки модалитети и ги споредувавме стапките на севкупното 5- и 10-годишно преживување кај вкупно 588 пациенти со ХЛ лекувани на Универзитетската клиника за хематологија во Скопје во текот на два последователни временски периоди, односно пред и по 2000 година. Вкупниот период на опсервација е од 1980 до 2020 година. Сите пациенти се на возраст над 14 години, со документирана пато-хистолошка дијагноза на ХЛ и со достапна медицинска документација, која содржи клинички и лабораториски податоци за состојбата при нејзиното појавување, ординираната терапија, како и во текот на натамошното следење на клиничката состојба на пациентите.

Резултати: Основните клинички карактеристики на анализираната популација во текот на двата временски периоди се споредливи со оние прикажани во релевантната медицинска литература, со само мали отстапувања. Стапката на 10-годишното севкупно преживување е подобрена за 31,7 % од едниот до другиот временски период. Во текот на двете последни декади од минатиот век (1980–2000), кај најголемиот број пациенти (94,7 %) прва тераписка опција биле COPP и сличните протоколи, со што е постигната ремисија на заболувањето кај 80 % од нив. По 2000 г. 95,8 % од новодијагностицираните пациенти биле третирани со хемотерапија од типот ABVD како прволиниски избор, при што стапката на постигнати комплетни ремисии изнесува 88,4 %. Ова ја потврдува супериорноста на протоколот ABVD во поглед на ефикасноста, подобрената контрола врз туморот и заболувањето, како и врз долгорочните клинички исходи. Додека во минатото имавме на располагање многу ограничени можности за згрижување на пациентите со релапсни и рефракторни (Р/Р) форми на ХЛ, анализата од третманот на ваквите пациенти со ХЛ лекувани со различни тераписки пристапи во текот на поскорешниот календарски период, го дефинира протоколот BEACOPP како преференцијален избор. Високодозната хемотерапија, следена со автологен графт од хематопоетски матични клетки, како стратегија за нашите пациенти со Р/Р форма на болест, во периодот по 2000 г. осигурува севкупно 5-годишно преживување за 51 % од нив, додека 45 % од нив преживуваат подолго од 10 години.

Заклучоци: Оваа анализа на базата на податоци за нашите пациенти со ХЛ покажува дека е постигнато огромно подобрување кај стапките на долгорочно преживување со настапувањето на новиот век. Во нашата институција постојано правиме напори во практиката да ги применуваме позитивните текови, како што препорачуваат релевантните упатства по однос на развојот и на напредокот кај дијапазонот на дијагностички постапки, лекувањето и севкупното згрижување на пациентите со ХЛ. Целта кон која се стремиме е обезбедување прогностички поволна витална статистика за популацијата наши пациенти, која сега достигнува преживување за 83,5 % на ниво од 10 години, што е многу споредливо со податоците што доаѓаат од поразвиените земји и центри. Во идните клинички студии ќе ја анализираме и ефикасноста на препаратот брентуксимаб ведотин, како и на новите PD-1 блокирачки антитела.

Клучни зборови: Хоџкинов лимфом, севкупно преживување, терапија, напредок