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Management Therapeutic Aspects in Hodgkin's Lymphoma in Children

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ABSTRACT

Hodgkin's lymphoma (HL), also known as Hodgkin's disease, is a neoplasia of the lymphoid tissue with a variable evolution, and a much-improved prognosis under the conditions of modern treatment. The histological characteristic of the disease is represented by multinucleated giant cells, Reed-Sternberg, located in an environment of inflammatory cells, namely small lymphocytes, histiocytes, neutrophils, eosinophils, plasma cells and fibroblasts. The tumor cells specific to the majority of Hodgkin's lymphoma cases (approximately 98%) are formed from the germinal center of B cells that are not capable of synthesizing immunoglobulins. Current treatment programs use therapy based on individual risk factors and response to treatment, in which patients are treated with multiple chemotherapy agents with or without low-dose loco-regional radiotherapy. The prognostic factors used in determining the intensity of chemotherapy are represented by the stage of the disease, the presence or absence of B symptoms (fever, weight loss, sweating), as well as the presence of bulky tumor masses. The treatment of Hodgkin's lymphoma is one of the success stories of modern medicine. Hodgkin's disease is among the curable forms of childhood cancer, with a 5-year survival rate that can reach a percentage of 98%. [1] In this paper, we followed the evolution of 76 patients with Hodgkin's lymphoma, hospitalized at the Fundeni Clinical Institute, between January 2005 and December 2015. These patients were diagnosed and treated according to current diagnostic and therapeutic protocols. A large part of the patients in the low-risk group showed a favorable response to the administration of the ABVD chemotherapy regimen, and the majority of patients in the intermediate and high-risk groups received combined chemotherapy regimens, with or without loco-regional radiotherapy, having a positive response to this therapeutic strategy. Retrospectively collected data were obtained from the analysis of patient observation sheets. These data include quantitative and qualitative variables. These represent the factors that influence or determine the development directions of each of the stages of the study. Quantitative variables are discrete (integer) or continuous (any value) - age, date of admission, number of leukocytes at diagnosis, number of various chemotherapy courses used in the treatment, period of follow-up of the effectiveness of the therapy (days, weeks, months, years), etc. Qualitative variables are ordinal or nominal – sex, environment of origin, presence or absence of general symptoms at diagnosis, histopathological diagnosis, response to treatment, complications, etc.

1. Introduction

Numerous combinations of chemotherapeutic agents are used in the treatment of LH. They differ according to certain criteria, among which the most important is represented by the stage of the disease. Combination therapy between several chemotherapeutic agents, especially in children, has been adopted to avoid the risk of cardiopulmonary toxicity, sterility and a second malignancy. Combined chemotherapy regimens are the treatment of choice in generalized forms of LH (stages IIIB, IVA, IVB). By introducing polychemotherapy, curability can also be discussed in the generalized forms of the disease.

To date, there are no concise indications for the implementation of hematopoietic stem cell transplantation (HSCT) as first-line therapy in HL, but patients in whom induction treatment has failed or in whom complete remission has been short-lived may benefit from transplantation of allogeneic, autologous marrow or autologous stem cells collected from peripheral blood. In bone marrow transplantation, approximately 50% complete remissions are obtained, of which 20-40% are long-lasting. [1]

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2. The purpose and objectives of the work

Purpose

The purpose of this work is to follow the clinical-biological evolution of a group of patients diagnosed with malignant Hodgkin's lymphoma and to establish the extent of the disease in order to place them in the appropriate risk groups for the individualization of current therapeutic procedures.

Objectives

1. Assessment of demographic characteristics
2. Histopathological characteristics and HL staging
3. Evaluation of the response to the treatment according to the risk group;
4. Event-free survival (EFS) and overall survival (OS) rates

2. Materials and methods

Type of study

The present study belongs to the category of descriptive observational studies, being carried out in a retrospective manner.

The studied population

The group included in this study is represented by 76 children and adolescents with Hodgkin's lymphoma who were diagnosed and treated in the Pediatric Clinic of the Fundeni Clinical Institute, Pediatrics I and Pediatrics II sections, between January 1, 2005 and December 31, 2015.

The collection of data necessary to achieve the proposed objectives was carried out by studying the observation sheets of patients with Hodgkin's lymphoma included in the study group.

Staging

The first step in achieving a correct and complete diagnosis was the classification in one of the 4 stages of the disease. These are highlighted in the table below according to Cotswold staging. [2]

Table I. Cotswold Staging

Stage	Lymphatic area involved
I	A single nodal group
II	Multiple ganglionic groups on the same side of the diaphragm
III	Multiple ganglionic groups on both sides of the diaphragm
IV	Multiple extranodal lymph node locations or extralymphatic disease
X	Bulk > 10 cm
E	Extralymphatic spread or isolated location of extranodal disease
A/B	**Symptoms B** : weight loss > 10%, fever, night sweats

Source: authors' contribution

Cotswold staging retains the original 4 clinicopathological stages of the Ann-Arbor classification, adding information on the prognosis of the disease according to the presence of "bulky" tumor masses (marked with X) and the extension to extralymphatic organs (marked with E) .

Table II. Classification of patients according to risk groups

The risk group	Patient characteristics
Low risk	Stages IA and IIA, without the presence of a mediastinal mass
Intermediate risk	Stages IA and IIA, with mediastinal mass Stages IB and IIB Stages IIIA and IVA regardless of absence or present mass mediastinal
Increased risk	Stages IIIB and IVB

Source: authors' contribution

3. Results

I. Demographic characteristics

Age

The average age of the group of patients included in the study was 12 years with a range between 0 and 19 years.

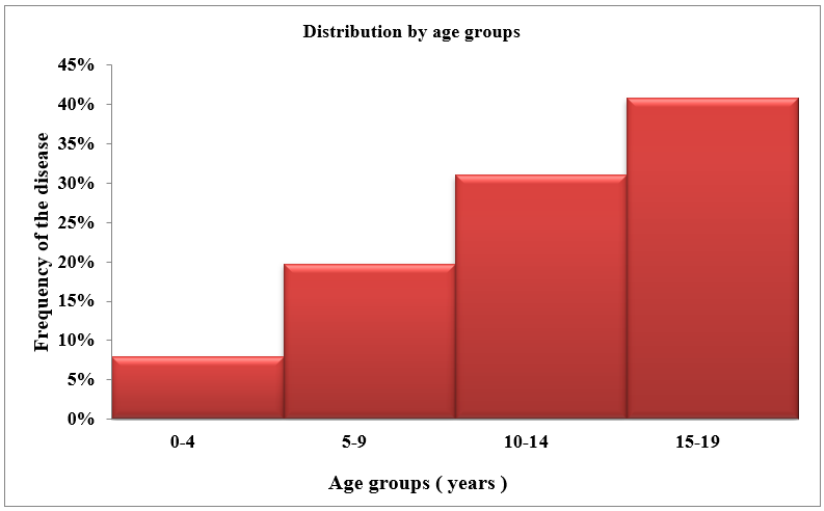

Chart No. 1

Source: authors' contribution

According to **Chart No. 1**, we observe a linear increase in the incidence of Hodgkin's lymphoma. In the range of 0-4 years, the prevalence of the disease is 8%, increasing to 20% in the age group 5-9 years. Followed by patients aged 10-14 with a percentage of 31%, the highest incidence of 41% being found in the 15-19 age range. The results of our study correlate with those in the specialized literature which claim that HL is rarely found among children under 4 years of age, while among adolescents there is a rapid increase in the incidence of the disease.

Sex

The number of cases included in the study totals 76, divided by sex, as follows in table III .

Table III. Number of patients according to sex

Sex	Number of cases	%
Female	37	49
Male	39	51

Source: authors' contribution

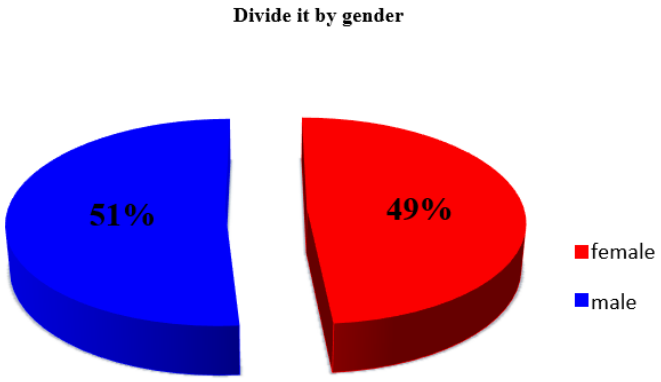

Chart No. 2

Source: authors' contribution

From the graph above, we observe an almost equal ratio between female (49%) and male (51%) HL patients, with a slight predominance of the male sex, a result that agrees with that in the specialized literature.

II. Histopathological characteristics and HL staging

Histological type

The breakdown by histological types is presented in the following table:

Table IV. The number of cases according to the histological type

Histological type	Number of cases			%
	Female	Male	Total	
Nodular sclerosis (NS)	24	24	48	63
Mixed cellularity (MC)	9	10	19	25
Lymphocyte depletion (LD)	2	3	5	6
Rich lymphocyte (RL)	1	1	2	3
Indefinite	1	1	2	3

Source: authors' contribution

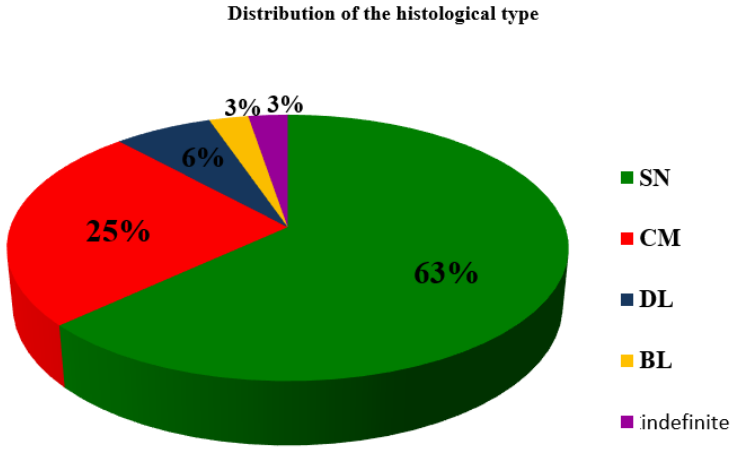

Chart No. 3

Source: authors' contribution

According to the previous graph, we note that the first place is occupied by the classic HL histological subtype with nodular sclerosis (NS) with a percentage of 63%. Classical HL with mixed cellularity (MC) is in second place and accounts for 25% of the total. Next, classic HL with lymphocyte depletion (LD) and lymphocyte rich (RL) with percentages of 6% and 3%, respectively. Also 3% of the total of histological forms identified are classified as an unclassifiable histological subtype.

The results expressed in our study are consistent with those in the specialized literature that differentiate the subtype with SN and that with CM as the most common forms of classic LH.

Stadialization

Ann-Arbor staging takes into account the following factors:

- the number of lymphatic areas involved;
- the topography of the areas in relation to the diaphragm;
- extra-lymphatic determinations;
- the presence of general signs B.

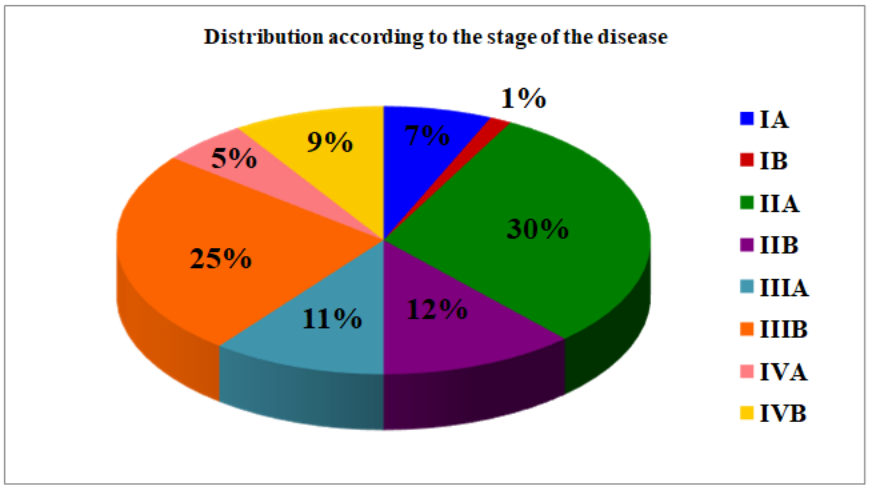

Chart No. 4

Source: authors' contribution

Stage IIA is the most common stage at the time of diagnosis, in the group of patients, with a percentage of 30%, followed by IIIB – 25%, IIB – 12%, IIIA – 11%, IVB – 9%, IA – 7 %, IVA – 5%, the last place being occupied by stage IB in a percentage of only 1%.

III. Treatment

Risk group

Table V. Number of patients according to risk group

Risk group	Total	
	Number	%
Low	13	17
Intermediate	37	49
High	26	34

Source: authors' contribution

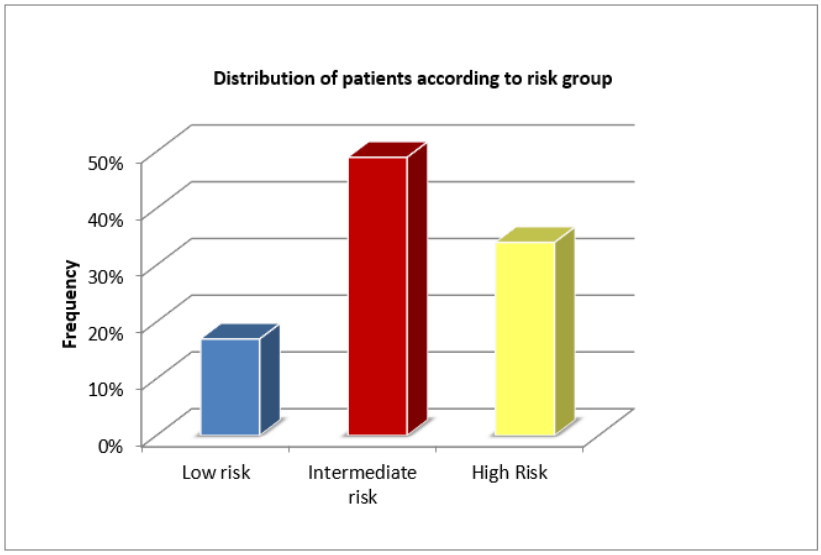

Chart No. 5

Source: authors' contribution

According to **Chart No. 5** and **Table V** , of all the patients included in our study, most of them fell into the intermediate risk group with a percentage of 49%. The second place is occupied by those in the increased risk group at 34%. Only 17% of the children were diagnosed in the low risk group.

Chemotherapy +/- Radiotherapy

The results of our study correlated with international ones regarding the application of radiotherapy (RT) in combination with chemotherapy regimens (CHT), which indicate the use of RT mainly in stages I and II, with a favorable prognosis (**Chart No. 6**).

Out of the total number of patients, 16 (21%) benefited from local RT, as follows:

- in the low-risk group, 7 patients (44%) received RT in combination with CHT;
- in the intermediate risk group, their number is 6 (37%);
- in the high risk group, the number is reduced to 3 patients (19%).

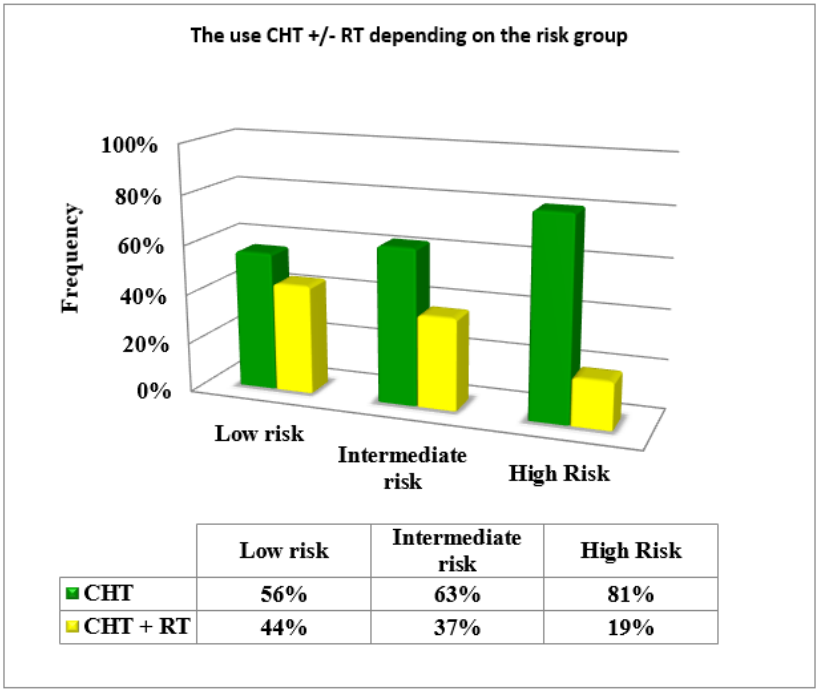

Chart No. 6

Source: authors' contribution

First line of treatment

Table VI. The first line of treatment according to the risk group

Risk group	Number of chemotherapeutic regimens – I line						
	ABVD	COPP/ABV	OEPA	BEACOPP	BEACOPP escalated	Combined CHT regimens	Total
Low	8	4	1	-	-	-	13
Intermediate	9	6	-	7	2	13	37
High	-	2	-	6	3	15	26
Total patients	17	12	1	13	5	28	76

Source: authors' contribution

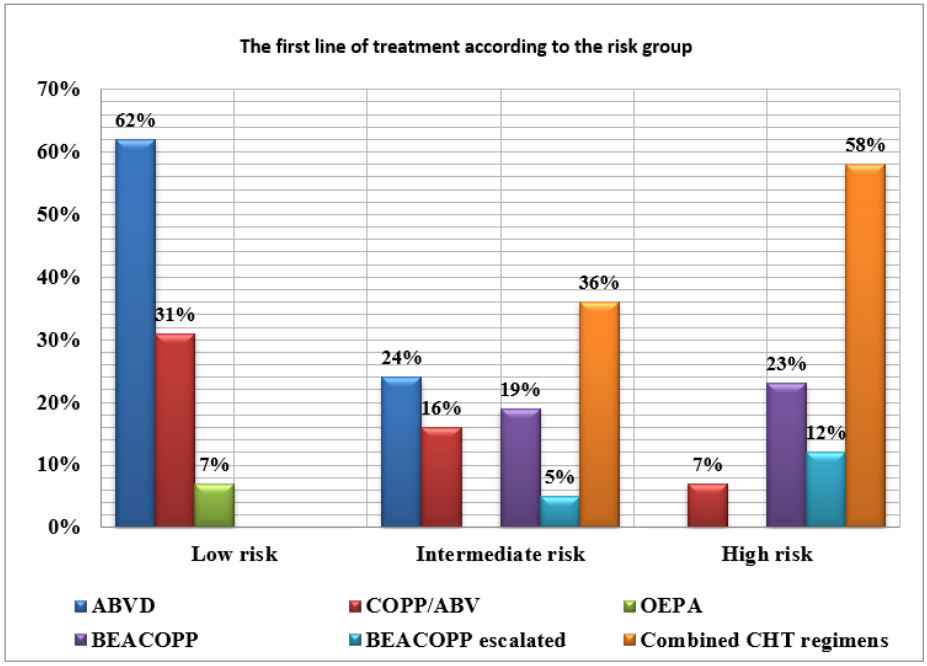

Chart No. 7

Source: authors' contribution

Chemotherapy regimens specific to the first line of treatment are presented in **Table VI** and **Chart No. 7**. We observe, in the low-risk group, the predominant use of monochemotherapy, while in the intermediate and high-risk groups, the use of combined chemotherapy predominates, which is also recommended in the international literature, especially in cases with a poor prognosis.

From the chart above, we note the use of the ABVD scheme by 62% in the low risk group and 24% in the intermediate risk group. In the high-risk group, this regimen was used only in combination with other regimens.

The COPP/ABV scheme is found in all risk groups, as follows: 31% in low risk, 16% in intermediate and 7% in high.

The OEPA scheme was used in combination with local RT only in the low-risk group, in 7% of cases.

A percentage of 19% of patients in the intermediate risk group, respectively 23% of those at high risk, benefited from the BEACOPP regimen. The escalated BEACOPP regimen was used in 5% and 12% respectively in the intermediate and high risk groups.

Polychemotherapy ranks first both in the intermediate risk group and in the high risk group in proportions of 36% and 58%, respectively.

Table VII. Results of response to first-line therapy

Response to first-line therapy	Total patients							
	Low risk		Intermediate risk		Increased risk		Total	
	Number	%	Number	%	Number	%	Number	%
Complete remission (CR)	12	92	25	68	13	50	50	66
Refractory disease	1	8	7	19	2	8	10	12
Early relapse	0	0	2	5	6	2. 3	8	11
Late relapse	0	0	1	3	4	15	5	7
Death	0	0	2	5	1	4	3	4

Source: authors' contribution

According to **Chart No. 8 and Table No. VII** , after first-line treatment, in the low-risk group, 92% of patients entered CR and 8% had treatment-refractory disease.

In the intermediate risk group, 68% achieved CR, 19% were unresponsive to first-line treatment, 5% and 3% experienced early and late relapse, respectively, and 5% died.

Of the high-risk group, 50% achieved CR and 8% had refractory disease. Those who suffered an early relapse are 23%, and those with a late relapse are 4%. Within this group, 4% died.

Thus, we observe that 66% of all patients entered complete remission (CR), 12% showed lack of response to treatment suggested by stationary/progressive disease. Early relapse and late relapse occurred in 11% and 7% of patients, respectively. 4% of patients died during the first line of treatment. Patients with refractory disease, early and late relapse total a percentage of 30% and have an indication for the second line of treatment, hematopoietic stem cell transplantation (HSCT).

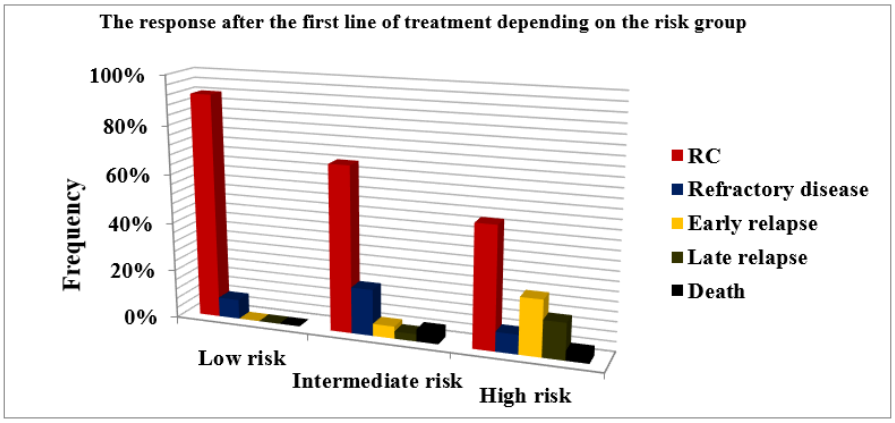

Chart No. 8

Source: authors' contribution

Next, we will present the indication for transplantation according to the corresponding risk group (**Chart No. 9**).

Second line of treatment (HSCT)

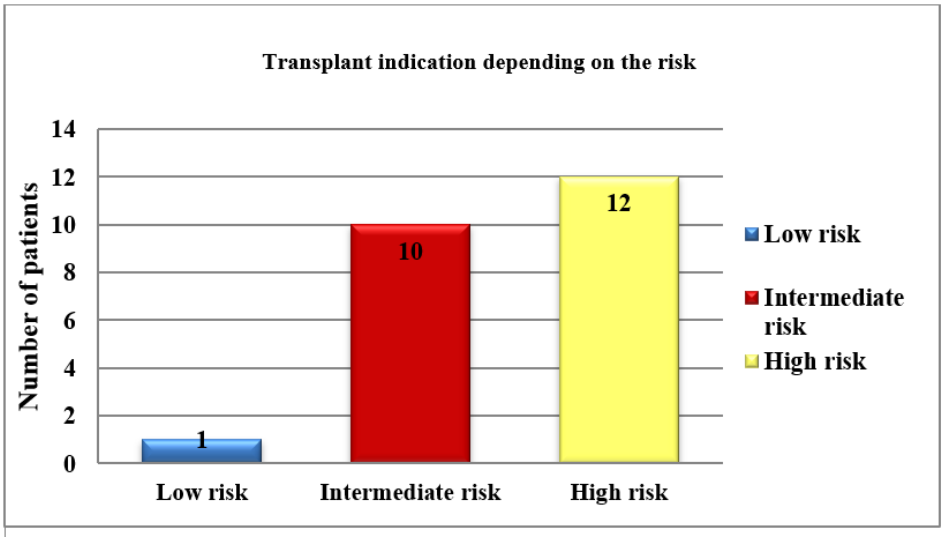

Chart No. 9

Source: authors' contribution

Of the 23 patients transplanted, 1 patient (4%) was in the low-risk group, 10 patients (43%) in the intermediate-risk group, and 12 patients (53%) in the high-risk group. These results agree with those in the literature that indicate the high-risk group with the most reserved prognosis, having frequent relapses or being refractory to polychemotherapy regimens, thus becoming candidates for bone marrow transplantation.

Table VIII. Results of response to second-line therapy

Response to second-line therapy	Total patients							
	Low risk		Intermediate risk		Increased risk		Total	
	Number	%	Number	%	Number	%	Number	%
CR	1	100	9	90	9	75	19	83
Death	0	0	1	10	3	25	4	17

Source: authors' contribution

Among the patients who benefited from HSCT, 100% of the patients in the low-risk group entered CR. In the intermediate risk group CR occurred in 90% of them, and 10% died posttransplantation. In the high-risk group, 75% achieved CR and 25% died (**Chart No. 10**).

Thus, we observe a total of 19 patients (83%) who entered the RC, and a number of 4 (17%) of them who died **(Table VIII).**

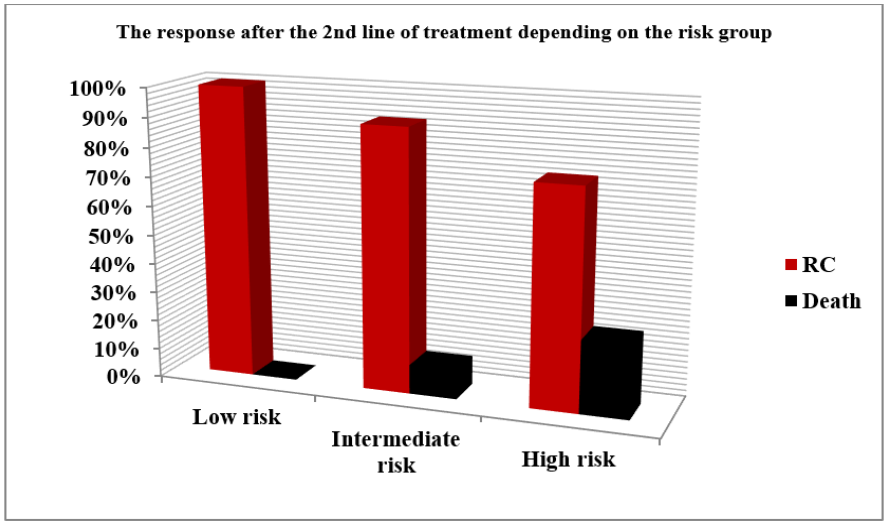

Chart No. 10

Source: authors' contribution

IV. Event-free survival (EFS) and overall survival (OS)

Table IX summarizes the evolution of the patients during the course of the study, the number of patients who completed the study in CR (with confirmation of the absence of metabolically active tumor lesions) and the number of deaths.

TABLE IX. Summary of the status at the end of the study

Risk group	Total		Completion of study in RC		Death	
	Number	%	Number	%	Number	%
Low	13	100	13	100	0	0
Intermediate	37	100	34	92	3	8
High	26	100	22	85	4	15

Source: authors' contribution

Table X shows the variation of OS and EFS for each risk group, and **Chart No. 11** and **No. 12** shows the overall survival and event-free survival curves.

Table X. Overall survival rates and EFS

Risk group	Overall survival (months)			EFS (Monday)		
	Min.	Max.	Mediate	Min.	Max.	Mediate
Low	36	36	36	15	36	22.5
Intermediate	2	24	8.3	2	35	15.5
Grown	2	31	12.8	2	34	13.5

Source: authors' contribution

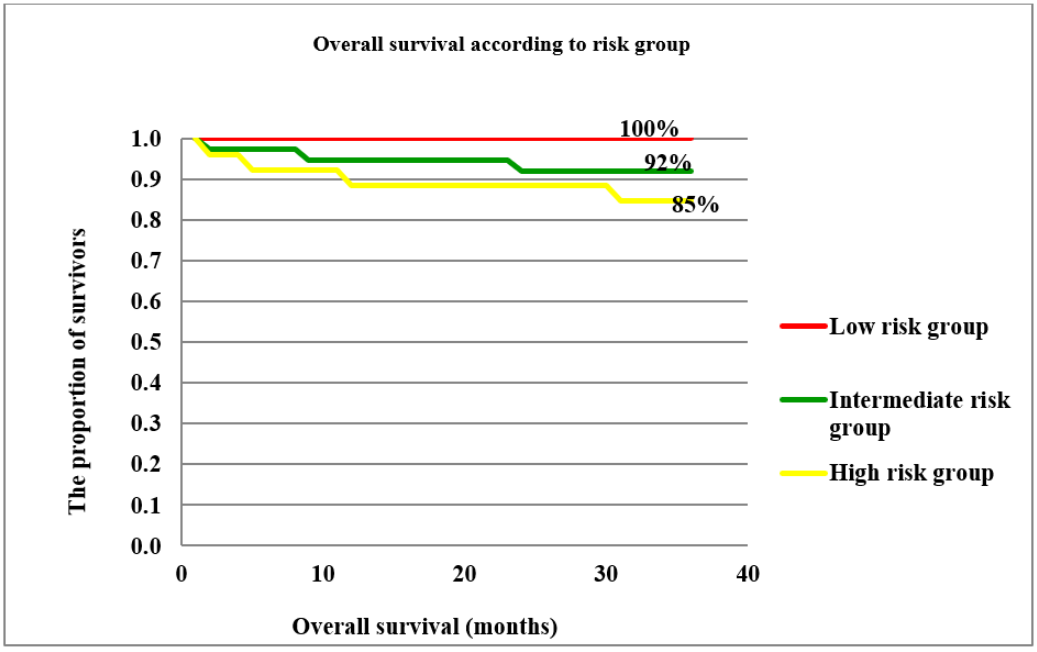

Chart No. 11

Source: authors' contribution

According to **Chart No. 11** , from a total of 76 patients, at the end of the last follow-up , the overall survival (OS) at 3 years (36 months) reached a percentage of 91%.

In the low-risk group, OS is 100%. In the intermediate and high risk groups, OS has a percentage value of 92% and 85%, respectively.

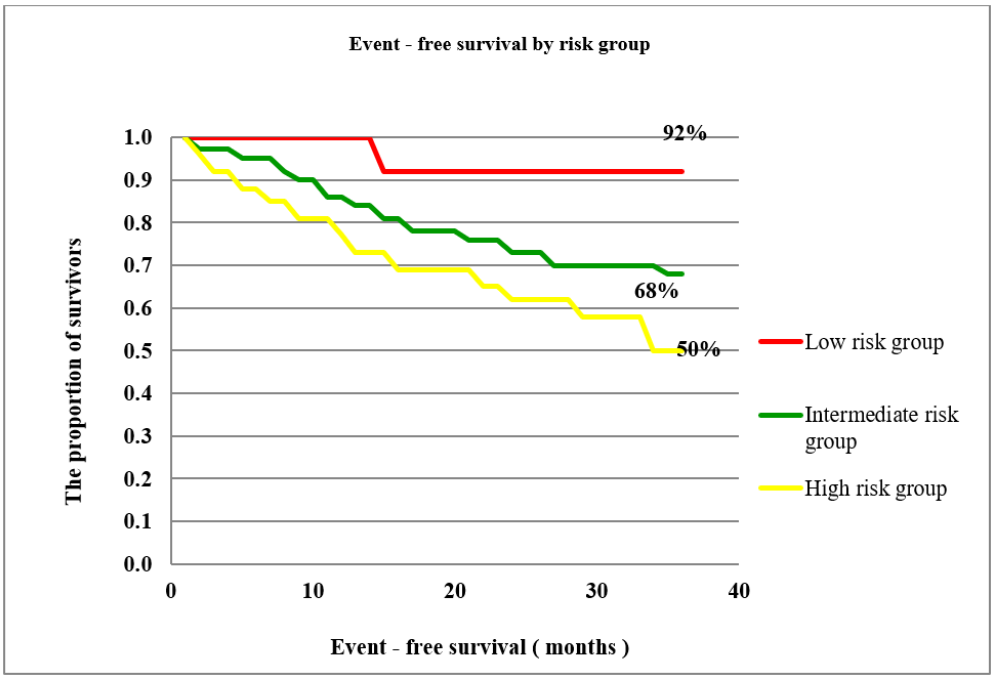

Chart No. 12

Source: authors' contribution

From **Chart No. 12** , we note that event-free survival (EFS) at 3 years is 66% in the studied group.

In the low-risk group, the EFS reaches a proportion of 92%. In the intermediate risk group, the EFS is 68%, and in the high risk group, it drops to 50%.

Discussions regarding the management of risk groups

Within the group of patients, the application of the therapy was carried out according to the three risk groups: low (13 patients), intermediate (37 patients) and high (26 patients). According to specialized literature [95], the association of radiotherapy (RT) with chemotherapy (CHT) is observed more frequently in stages I and II, with a favorable prognosis that falls into the low-risk group, as follows: in the low-risk group 7 patients (44%) received RT in association with CHT, in the intermediate risk group, their number is 6 (37%), in the high risk group, the number is reduced to 3 patients (19%). A decrease in the use of RT is observed in advanced stages.

The first line of treatment was based on the use of single therapeutic regimens or in combined regimens, depending on the belonging to the corresponding risk group of each patient.

In the low-risk group, the main chemotherapy regimen used was ABVD, in 62%. This was administered in 4-6 cycles, repeated every 28 days. In second place, with a percentage of 31%, is the COPP/ABV scheme with an administration frequency identical to that mentioned in the ABVD scheme. One patient (7%) received the OEPA regimen, 2 cycles, every 28 days. 12 of the 13 patients in this group achieved complete remission (CR) after first-line therapy. Only one patient, who was treated with the ABVD regimen, presented with progressive disease, fulfilling the conditions for the administration of second-line therapy (HSCT).

In the intermediate risk group, the use of polychemotherapy regimens was preferred by 36%. 24% of patients received the ABVD regimen, 19% received the BEACOPP regimen administered in 4-8 cycles, repeated every 21 days. The COPP/ABV regimen was used in 16% of cases and escalated BEACOPP in 5% of patients. The escalated BEACOPP schedule is repeated every 21 days, with a frequency of 2-6 cycles, alone or in combination with 2-6 ABVD/BEACOPP cycles. From this risk group consisting of 37 patients, 25 entered CR, in 7 of them there was a lack of response to treatment, 3 relapsed (2 – early, 1 – late), being viable candidates for TCSH, and 2 patients died.

In the high-risk group, polychemotherapy was used in 58% of cases. BEACOPP and escalated BEACOPP regimens were administered to 23% and 12% of patients, respectively. Only 7% of them received the COPP/ABV scheme. Among the 26 patients in the group, 13 achieved CR, 2 patients presented refractory disease, 10 suffered relapses (6 – early, 4 – late), falling within the indications for the administration of the second line of treatment and 1 patient died.

The polychemotherapy regimens used represent combinations of simple schemes, adapted to the particularities of each patient, according to body weight, disease stage and periodic monitoring. [3]

So, at the end of the first line of treatment 50 patients achieved CR, 3 patients died and 23 patients (30%) received the indication of HSCT. Of these, 1 patient (4%) was in the low-risk group, 10 patients (43%)

in the intermediate-risk group, and 12 patients (53%) in the high-risk group. These results agree with those in the literature that indicate the high-risk group with the most reserved prognosis, having frequent relapses or being refractory to polychemotherapy regimens, thus becoming candidates for bone marrow transplantation. [4]

Conclusions

1. The study confirmed in the group of patients analyzed **the distribution by age groups** reported at the international level, with the reduced incidence of children under 4 years (8%) and an increase in the incidence of the disease in adolescents (15-19 years) (41%), as well as a higher age at diagnosis for females (13.7 years), compared to males (11 years).
2. Among the 4 highlighted **histological types** , the major prevalence of classical Hodgkin's lymphoma with nodular sclerosis (NS) (63%) is confirmed, more frequently found in adolescents, the second place goes to the histological subtype with mixed cellularity (MC) (25%) , diagnosed in a higher proportion in children under 14 years of age. Classic Hodgkin lymphoma, lymphocyte-rich (RL) (3%) and lymphocyte-depleted (DL) (6%) were rare.
3. At the time of diagnosis, most of the patients were in stages II and III of **the Ann-Arbor classification** (78%).
4. Thus, **the first-line treatment** was applied according to the three risk groups. In the low-risk group, the use of monochemotherapy was preferred , the ABVD regimen being predominant (62%), in combination with radiotherapy (RT), and in the intermediate and high-risk groups, the use of combined chemotherapy regimens prevailed (ABVD/ COPP-ABV/ BEACOPP/ escalated BEACOPP) (36% and 58%, respectively) associated with a better response of patients in advanced stages of the disease. RT administration in these cases was carried out individually according to the evolution of each patient. A better response to first-line therapy was observed in patients with stage I and II disease, while advanced stages were more frequently associated with refractory disease or relapses.
5. **Second-line treatment (autologous stem cell transplantation)** was applied to patients who did not respond to first-line therapy, to those who suffered early relapses and late relapses, regardless of risk group (30% of patients).
6. **The overall survival (OS)** of the cohort was 91% at the end of the last follow-up , and the **event-free survival (EFS)** rate was significantly lower at 66%.
7. The present study thus confirms the importance of diagnosing Hodgkin's lymphoma in the early stages and correctly classifying it in the appropriate risk group in order to apply optimal individualized therapy. Due to the major influence of these characteristics on the prognosis, it is necessary to continue the process of adjusting the therapeutic behavior aimed at minimizing the toxic effects in patients with a favorable prognosis and increasing the chance of long-term survival of cases with a reserved prognosis.

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