The Effects of the Therapeutic Regimen Used in Hodgkin Lymphoma and the Correlation with Prognosis Factors

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The Hodgkin lymphoma treatment is adapted to the disease type, disease stage and to an evaluation of the risk. The treatment is focused on the adjustment of the therapy to each patient depending on the age, toxicity risk on short and long term and the relapse risk. The study proposes the evaluation of the response to the treatment further to the administration of different therapeutic regimens as well as the correlation with the negative diagnosis factors of Hodgkin lymphoma. This is a retrospective study on 71 patients diagnosed with Hodgkin lymphoma in the Hematology Department of Timisoara between January 2014 and December 2017. The data obtained have been collected from a database and processed with the SPSS 20.0. software . In our study there were included 71 patients diagnosed with Hodgkin lymphoma with a medium age of 42.12±16.45 years old. By the time of the diagnosis, the patients showed the following hematological, biochemical and immunological parameters. The response to treatment is influenced by the presence of the negative prognosis factors : the age of ≥40 years old, extralymphatic infiltration, VSH > 50mm/h , presence of general B signs, more than 3 lymph node sites affected, bulky disease and Ann-Arbor III and IV stages. The treatment of Hodgkin lymphoma is guided by the traditional clinic prognostic factors and by the laboratory which often represent a substitute marker for the biological characteristics which many times are not included in the standard evaluation.

Keywords: Hodgkin Lymphoma, treatment, Bortezomib Vedotin, prognostic factors

There was made a great progress in the treatment of the Hodgkin lymphoma (LH) during the last years. The recovery rates have been found at 80-90% of the patients, and LH is among the neoplastic diseases which indicate the best results on long term after the chemo-therapy.However, 15-20% of the patients will develop therapy resistance or they will usually show a relapse in the first two years [1].

The Hodgkin lymphoma treatment is adapted to the disease type, disease stage and to an evaluation of the risk. The Hodgkin lymphoma is considered to be a a curable malignity, but the therapies for this disease could cause significant toxicity on long term. The general treatment methods include radiotherapy, induction chemotherapy, salvage chemotherapy and stem cell transplant.

Experimental part

The treatment is focused on the adjustment of the therapy to each patient depending on the age, toxicity risk on short and long term and the relapse risk.

The induction therapy contains several types of therapeutic regimens which will be adapted to the patient features..

The MOPP regimen is administrated every 28 days in 6 or more cycles as follows:

-Mechlorethamine: 6 mg/m^2, days 1 and 8
-Vincristine: 1.4 mg/m^2, days 1 and 8
-Procarbazine: 100 mg/m^2, days 1-14
-Prednisone: 40 mg/m^2, days 1-14 only in cycle 1 and 4

The ABVD regimen is administrated every 14 days in 6 or more cycles as follows:

-Adriamycin: 25 mg/m^2, days 1.15
-Bleomycin: 10 mg/m^2, days 1.15
-Vinblastine: 6 mg/m^2, days 1. 15
-Dacarbazine: 375 mg/m^2, days 1.15

The Stanford V regimen is administrated as follows [2] :

-Vinblastine: 6 mg/m^2, weeks 1, 3, 5, 7, 9, 11
-Doxorubicin: 25 mg/m^2, weeks 1, 3, 5, 9, 11
-Vincristine: 1.4 mg/m^2, weeks 2, 4, 6, 8, 10, 12
-Bleomycin: 5 units/m^2, weeks 2, 4, 8, 10, 12
-Mechlorethamine: 6 mg/m^2, weeks 1, 5, 9
-Etoposide: 60 mg/m^2 twice a day , weeks 3, 7, 11
-Prednisone: 40 mg/m^2, in any other day, weeks 1-10, short weeks 11, 12
-Associated radiotherapy in the weeks 2-4 after the chemotherapy completion

The escalated BEACOPP regimen is administrated at interval of 3 weeks in 8 cycles as follows:

-Bleomycin: 10 mg/m^2, day 8
-Etoposide: 200 mg/m^2, days 1-3
-Doxorubicin: 35 mg/m^2, day 1
-Cyclophosphamide: 1.250 mg/m^2, day 1
-Vincristine: 1.4 mg/m^2, day 8
-Procarbazine: 100 mg/m^2, days 1-7
-Prednisone: 40 mg/m^2,days 1-14

The Salvage chemotherapy

If the induction chemotherapy is not successful or if relapse occurs, the salvage chemotherapy is required as it

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includes complementary molecules. These are the most used regimens:

-ICE (ifosfamide, carboplatin, etoposide)

-DHAP (cisplatin, cytarabine, prednisone)

-ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)

The ICE regimen is administrated as follows:

-Ifosfamide: 5 g/m^2, day 2

-Mesna: g/m^2, day 2

-Carboplatin: AUC 5, day 2

-Etoposide: 100 mg/m ^{2}, days 1-3

The DHAP regimen is administrated as follows:

-Cisplatin: 100 mg/m^2, day 1

-Cytarabine: 2 g/m^2, twice on day 2

·-Dexamethasone: 40 mg, days 1-4

Purpose: The study proposes the evaluation of the response to the treatment further to the administration of different therapeutic regimens as well as the correlation with the negative diagnosis factors of Hodgkin lymphoma..

Methodology:

I made a retrospective study on 71 patients diagnosed with Hodgkin lymphoma in the Hematology Department of Timisoara between January 2014 and December 2017.The main method to establish the diagnosis was the biopsy followed by the histopathological examination and immunohistochemistry of the sampled tissue. The stage has been determined by means of computerized tomography (CT). The polychemotherapy protocol and the number of cycles performed were decided based on the disease histological stage and degree. The patients data and their medical history data as well as the results of the laboratory tests performed have been collected from the patients' medical files.

There have been used treatment protocols for line I, line II and line III as per the international guidelines and namely:

I.Treatment of line 1

A. Classic LH stages I-II favorable (no negative prognostic factors) : ABVD, 4 treatment cycles + RT 30-36 Gy

B. Classic LH stages I-II unfavorable (at least one negative prognosis factor): ABVD, 6 treatment cycles + RT 30-36 Gy 2.

C. IIB stage with *bulky* mass and /or extra lymphatic infiltration is considered *advanced* (according to ESMO) and the treatment could be administrated as follows: 4 cycles of escaladated BEACOPP + 4 cycles of BEACOPP + RT 30-36 Gy

D. Classic LH stages III-IV

1. ABVD, 8 courses of treatment , or

2. 4 cycles of escaladated BEACOPP, followed by 4 cycles of BEACOPP

3. 30-36Gy radiotherapy if there existed initially bulky masses or if after the 8 courses of treatment, residual masses >1.5 cm still exist.

4. The patients >60 years old : the ABVD treatment protocol is prefered given that the BEACOPP treatment provide a higher toxicity.

5. For patients <60 years old, the following characteristic features would direct the treatment towards BEACOPP rather than ABVD:- Stage IV - Albumin <4g/dL - Leucocytes >15.000/c.mm - Lymphocytes <6% - Hgb<10g/dL - Sex Male - Age > 50 ani

E. Nodular LH lymphocyte predominant:

1. Stagel IA - after the ablation of the concerned lymph node, expectance can be chosen

2. Other stages - identical attitude with LH classic - There can be added rituximab, 375mg/m^2 in day 1 of each chemotherapy course of treatment [3-6]

II.Treatment of Line II

A. Treatment indications for Line 2:

1. Lack of clinic response after 2-3 chemotherapy courses of treatment

2. Lack of complete response (clinic and PET-CT/CT) at intermediate balance (after 4 cycles of treatment)

3. Relapse in <12 months since having obtained a complete response

4. Relapse in >12 months, but with stages III-IV, bulky mass and/or general signs

5. In case of relapse in >12 luni, but with stage I-II, with no bulky mass and no general signs - the initial chemotherapy regimen can be used

The line 2 chemotherapy regimens are: 1. DHAP/ ICE/ IGEV, GVD, 4 courses of treatment followed by high-dose (BEAM) chemotherapy + stem cell autotransplant [7-8]

III.The line 3 treatment is used in case of the second relapse occurrence or if the disease is refractory to 2 lines of treatment:

1.There can be used a line 2 regimen which has not been used previously

2. High dose chemotherapy + autotransplant (if not previously made)

3.Stem cell allogreffe

4. *Metronomic* treatment - cases where the above mentioned methods are not efficient or they cannot be applied – PEP-C [9-10] regimen

Statistical analysis

The data obtained have been collected from a database and processed with the SPSS 20.0. software . There were calculated the anthropometric, hematological, biochemical immunological parameters, the therapy applied and the response to the therapy . For the descriptive statistics purpose, the results were expressed in percentage and absolute values.

Results and discussions

In our study there were included 71 patients diagnosed with Hodgkin lymphoma with a medium age of 42.12±16.45 years old where the youngest patient was 18 years old and the oldest patient was 81 years old. Most of the patients are men (45 men and 26 women).

By the time of the diagnosis, the patients included in the study showed the following hematological, biochemical and immunological parameters (table 1).

As for the histological form, most of the patients showed nodular sclerosis [39] and mixed cellularity [28].

19 patients from the total of 71 showed bulky disease,while 27 of the 71 ones showed extra lymphatic infiltration in one or more sites.

Most of the patients (46.5%) were diagnosed late, in stage IV of the disease, according to Ann- Arbor classification, very few in stage I (8%), and the remaining 45.1% being diagnosed in stages II and III of disease (32 patients).

Thus, there was differentially established a first line treatment according to the therapeutic protocol for the patients in different stages of disease.

As response to line 1-26 patients were in complete remission, 15 patients in partial remission, the disease was in progression for 13 patients, 14 patients relapsed and 3 died.

36 of the patients with unfavorable evolution continued in a differential manner, the second line treatment according to the therapeutic protocol.

However, of the 36 patients, 10 patients died , 9 show complete remission , and the remaining 17 are in partial remission, progressive disease or relapse.

Table 1
DISTRIBUTION OF PATIENTS BASED ON THEIR HEMATOLOGICAL, BIOCHEMICAL AND IMMUNOLOGICAL PARAMETERS

Parameter	Value	Frequency	Percent
Hemoglobin (g/dl)	<10.5	19	26.8
	10.5-13	28	39.4
	>13	24	33.8
Leucocytes (/mm^3)	<4000	7	9.9
	4000-10000	45	63.4
	>10000	19	26.8
Lymphocytes (/mm^3)	<600	12	16.9
	600-1000	10	14.1
	1000-3000	43	60.6
	>3000	6	8.5
Monociytes (/mm^3)	<1000	38	53.5
	1000-1500	20	28.2
	>1500	13	18.3
Eosinophiles (/mm^3)	<500	44	62.0
	500-1000	19	26.8
	>1000	8	11.3
Blood platelets (/mm^3)	<150000	5	7.0
	150000-400000	58	81.7
	>400000	8	11.3
VSH (mm/h)	<30	11	15.5
	30-49	31	43.7
	>50	29	40.8
Fibrinogen (mg/dl)	<400	36	50.7
	>400	35	49.3
FAS (U/l)	level up	17	23.9
	normal	54	76.1
Uric acid (mg/dl)	<2.4	10	14.1
	2.4-5.7	29	40.8
	>5.7	32	45.1
LDH (mg/dl)	normal	11	15.5
	level up	60	84.5
Ferritine	level up	37	52.1
	normal	34	47.9
Serum albumin (g/dl)	<3.5	47	66.2
	3.5-5	17	23.9
	>5	7	9.9

Table 2
DISTRIBUTION OF PATIENTS BASED ON THE HISTOLOGICAL FORM

		Frequency	Percent
Form	Mixed cellularity	28	39.4
	Nodular sclerosis	39	54.9
	Predominantly lymphocytic	4	5.6
	Total	71	100.0

Table 3
DISTRIBUTION OF PATIENTS DEPENDING ON THE DISEASE STAGE

		Frequency	Percent
Stage	I	6	8.5
	II	18	25.4
	III	14	19.7
	IV	33	46.5
	Total	71	100.0

Table 4
DISTRIBUTION OF PATIENTS ACCORDING TO THE FIRST LINE TREATMENT AND RESPONSE TO THE TREATMENT

			Response to first line treatment					Total
			Complete remission	Partial remission	Progressive disease	Relapse	Death	
First line treatment	ABVD 3 cycles +radiotherapy	Count	3	3	1	3	0	10
		%	30.0%	30.0%	10.0%	30.0%	0.0%	100.0%
	ABVD 6 cycles	Count	21	9	12	6	2	50
		%	42.0%	18.0%	24.0%	12.0%	4.0%	100.0%
	BEACOPP escaladated	Count	2	3	0	4	0	9
		%	22.2%	33.3%	0.0%	44.4%	0.0%	100.0%
	BEACOPP	Count	0	0	0	1	1	2
		%	0.0%	0.0%	0.0%	50.0%	50.0%	100.0%
Total		Count	26	15	13	14	3	71
		%	36.6%	21.1%	18.3%	19.7%	4.2%	100.0%

Table 5
DISTRIBUION OF PATIENTS BASED ON THE SECOND LINE TREATMENT AND THEIR RESPONSE TO THE TREATMENT

			Response to second line treatment					Total
			Complete remission	Partial remission	Progressive Disease	Relapse	Death	
Line 2 of treatment	BEACOPP escaladated	Count	3	2	1	4	3	13
		%	23.1%	15.4%	7.7%	30.8%	23.1%	100.0%
	BEACOPP	Count	3	1	1	2	2	9
		%	33.3%	11.1%	11.1%	22.2%	22.2%	100.0%
	ESHAP	Count	3	1	0	0	2	6
		%	50.0%	16.7%	0.0%	0.0%	33.3%	100.0%
	IGEV	Count	0	1	1	3	3	8
		%	0.0%	12.5%	12.5%	37.5%	37.5%	100.0%
Total		Count	9	5	3	9	10	36
		%	25.0%	13.9%	8.3%	25.0%	27.8%	100.0%

			Response to line 3 of treatment			Total
			Complete remission	Partial remission	Death	
Treatment line 3	Brentuximab Vedotin	Count	5	2	6	13
		%	38.5%	15.4%	46.2%	100.0%
	ESHAP	Count	1	0	1	2
		%	50.0%	0.0%	50.0%	100.0%
Total		Count	6	2	7	15
		%	40.0%	13.3%	46.7%	100.0%

Table 6
DISTRIBUTION OF PATIENTS BASED ON THE 3RD LINE OF TREATMENT AND THEIR RESPONSE TO THE TREATMENT

15 of these patients continued the 3rd line of treatment , in case of 13 of them the treatment was followed by Brentuximab Vedotin treatment and 2 of them with l ESHAP regimen.

7 of them died during the treatment , while the remaining 8 patients showed partial or complete remission.

The response to treatment is influenced by the presence of the negative prognosis factors which in case of Hodgkin lymphoma are the age of ≥40 years old , extralymphatic infiltration by contiguity, VSH > 50mm/h ,presence of general B signs (except for stage I) , more than 3 lymph node sites affected, big tumor *bulky* disease and Ann-Arbor III and IV stages. The presence of one single factor of those mentioned above is sufficient for the patient to be considered an unfavorable case (table 7).

In our study, the response to the first line of treatment is significantly correlated from statistical point of view, with the disease stage, namely an unfavorable response in stages III and IV , the presence of constitutional symptoms and a VSH over 50 mm/h. The patients with negative response to the first line of treatment and who were included in the second line of treatment present, as negative prognostic factor which significantly correlates from statistical point of view with an unfavorable response to the second line of treatment too, the VSH over 50mm/h.

As for the third line of treatment where there were included only 15 patients of the study, the response was unfavorable, 46.7% of the patients died. As negative prognostic factors which influenced the response to the third line of treatment, were the disease stage, taking into account that the patients included in the third line of treatment were in stage IV and the extra lymphatic infiltration. There exists a strong significant statistical correlation between these factors and the

There are many prognostic factors available in HL. Their evaluation even since the beginning of the disease is important so that to include the patients in different categories of risk and to adjust their treatment in order to get as favorable response as possible. In our study we evaluated as risk factors with negative prognosis , the extension of the disease, the age, extralymphatic infiltration, presence of tumor mass, disease stage, VSH and the presence of B type symptoms.

The extension of the disease and the tumor mass are the most important characteristics of the disease which are used to stratify the therapy strategies. [11] In case of a limited stage of disease, the presence of a bulky mass detected by the mediastinal radiography or CT at staging, is considered a negative predictor of the response to the treatment [12] Instead, in the advanced stage of the disease, the presence of bulky tumor is not a risk factor according to the international scoring of prognosis (IPS) for HL [13]. As the measurement of the volume is limited to the unique biggest mass , it could underestimate the total tumor burden in case of patients with diffuse disease. The newer methods for measuring the tumor burden can provide a more precise estimate of the tumour volume [14-15]. The complexity of the examination of all lesions in any section of the scan with the decrease of the normal structures which are present in the tumor tissue and the approximation of the bone marrow implication, limited the application to a larger extent of this evaluation type. The HL spreading beyond its micro-environment of lymph nodes to the extralymphatic organs is associated to a poor result. In the limited stage, the infiltration of a extra node site is defined as a risk factor by the GSHG scoring system. For the patients found in an advanced stage of the disease, the diffuse infiltration of the organs in stage IV is an independent risk factor in IPS [16-17]. In our study the extralymphatic infiltration and the presence of bulky tumor mass correlate with an unfavorable response to the

Table 7
CORRELATION BETWEEN THE RESPONSES OF TREATMENT AND ALL THE FACTORS INVOLVED

		age	Stage	Bulky disease	Extra nodular affectation	VSH	Symptoms type B
Response to line 1 of treatment	Pearson Correlation	.158	.249*	.186	-.103	.392**	.270*
	Sig. (2-tailed)	.188	.036	.120	.392	.001	.023
	N	71	71	71	71	71	71
Response to line of treatment	Pearson Correlation	.030	-.056	.020	-.212	.411*	.007
	Sig. (2-tailed)	.861	.745	.906	.215	.013	.966
	N	36	36	36	36	36	36
Response to line 3 of treatment	Pearson Correlation	.122	.612*	.149	-.574*	.511	.141
	Sig. (2-tailed)	.664	.015	.596	.025	.051	.617
	N	15	15	15	15	15	15

treatment even if there is no other statistical significance than the response to the third line of treatment.

Another particularly important factor is the age. It impacts the prognosis in at least two manners, on one hand, it is intrinsically associated with the HL biology and on the other hand, the old age is often associated with low comorbidity and tolerability of the chemotherapeutic regimens used for younger patients, such treatment can be also model for targeted drug delivery systems[25]. The HL epidemiology is characterized by a bimodal distribution by ages . Further to the peak from the age of 20 of young adults, there exists a second increase of the incidence , particularly for the men, after the age of 50-55 . Compared to other neoplastic hematological diseases which usually establish a cut-off to define the patients as old when reaching their 60 , the cut-off in case of HL is moving towards a younger age.

In the International Prognosis Score for the patients with a disease of advanced stage , the age goes down to 45 years.The EORTC considers the age of more than 50 years a risk factor for the patients whose disease is in a limited stage. The older age is associated with a higher frequency of the histotype of the mixed cellularity and of the EBV presence in the neoplastic cells compared to younger patients [18]. The EBV association seems to be a negative prognostic factor for old patients.[19-21]. It is assumed that the loss of the immunological control of the EBV infected cells could contribute to the development of HL associated with EBV at the old patients. The aging of the immunitary system (immunosenescence) is characterized by the reduced function of the immune adaptative response which includes the T and B cell function. It has not been determined yet whether the immunosenescence is a mechanism of the HL pathogenesis in elderly and whether it contributes to the negative impact on the prognosis. The HL therapy for elderly is often complicated by the toxic side effects of the chemotherapy. The standard treatment with ABVD is not often recommended for the patients over 70 years. Bleomicin determines an increased frequency of the pulmonary toxicity. A recent report indicated that the incidence of the pulmonary toxicity with the bleomicin amounted to 32%, with a death rate of 25 % [22]. Neither is the BEACOPP regimen recommended for the patients over 60 and in advanced stages of the HL.[23;24]. It has been found out that in such cases, the death rate amounted up to 13.3% .[26] The therapy for the old patients with HL remains a challenge and there is still missing an efficient therapy with acceptable toxicity levels. The availability of monoclonal antibodies like Brentuximab, may represent a major step forward. In our study no statistical significant correlation was revealed between the age and response to the treatment and most likely this is due to the patients' average age of less than 42 of our study.

The systemic symptoms represented by an unexplainable fever of > 38 ° C, night sweats and loss of weight (> 10% of weight) are found at about 10-25% of the patients with limited disease stages and up to 70% of the patients in advanced stage [27]. Among the symptoms, the isolated night sweats do not seem to be associated to poor results. The presence of B symptoms constitute a risk factor particularly in stage II of the bulky disease which is not considered a limited disease stage by the German Hodgkin study group when B symptoms are present.

The B symptoms are caused by the production of proinflammatory cytokines by Hodgkin tumorous tissue particularly IL-1, TNF-alfa and IL-6. The B symptoms are associated to a variety of laboratory abnormalities. The presence of B symptoms at the diagnosis establishment seem to be a negative prognostic factor and in our study, too, there is a significant correlation, from statistics point of view, between their presence and the unfavorable response to the first line of treatment.

Conclusions

In conclusion, the treatment of Hodgkin lymphoma is guided by the traditional clinic prognostic factors and by the laboratory which often represent a substitute marker for the biological characteristics which many times are not included in the standard evaluation. There is not currently any consensus regarding the way of integrating these biological markers as accepted clinic prognostic risk factors in prognosis scores or regarding how to use this information to adjust the treatment. It still remains a challenge to identify the best parameters playing a part in the prognosis prediction in case of a single patient and to identify the significant group of patients for whom the standard treatment is not enough.

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