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Article / Artigo

Hodgkin's lymphoma in children and adolescents: 15 years of experience with the DH-II-90 protocol

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*The challenge of new protocols for treatment of HL is to decrease its toxicity, without impairing results. The protocol DH-II-90 was designed to treat children and adolescents with HL. The objectives of this work were: 1) to assess the overall and event free survival of patients with newly diagnosed HL treated with the DH-II-90 protocol, 2) to assess the overall and event free survival by stage, age, presence of bulky disease, mediastinal mass, B symptoms, dose and type of radiotherapy, and 3) to describe late effects data collected from the patients´charts. Sixty eight patients with HL, from 0 to 21 years of age (median age 9 yr, 20F:48M) were treated with ABVD and involved-field radiotherapy for low risk patients, and ABVD plus MOP or COP and extended field radiotherapy for high risk patients. Stage distribution was: nine (13.2%) stage I A; 29 (42.6%) II A; five (7.4%) II B; nine (13.2%) III A; ten (14.7%) III B; two (2.9%) IV A and four (5.9%) IV B. The 10-year overall survival was 96.1% ± 3.8 for the low risk group and 93.3% ± 4.5 for the high risk group (p= 0.402). The 10-year event free survival was 88.9% ± 5.2 for high risk and 86.5% ± 6.3 for low risk patients (p= 0.969). The presence of mediastinal mass and more than 2100 cGy radiation doses had negative impact on event free survival (p= 0.020 and p= 0.014 respectively).Thyroid gland dysfunction was frequently observed, with two cases of thyroid carcinoma. The DH-II-90 protocol is effective, but the late effects presented by this group of patients require further modifications on therapy schedule. Rev. Bras. Hematol. Hemoter. 2010;**32**(4):295-302.*

Keywords: *Hodgkin lymphoma;child; chemotherapy; radiotherapy; survival.*

Introduction

Hodgkin's lymphoma (HL), now recognized as a malignant disease originating in the lymphatic and reticuloendothelial systems, is a cancer that has good prognosis in the pediatric population.[1,2] The combination of chemotherapy and radiotherapy has given excellent results in HL for more than 30 years. In the past, the age or maturity of the patient was not taken into account in treatment planning, which included high-dose radiotherapy (3500-4400 cGy) over extensive territories. This strategy led to high cure rates, but over time, sequelae, such as growth inhibition of the irradiated tissue and secondary malignancies that suggested that doses and fields should be reduced, but at the same time maintaining the same high cure rates. Today, some programs attempt to eliminate radiotherapy in children by increasing the aggressiveness of the chemotherapy regimens, especially for patients with

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localized disease. For patients with advanced disease, however this approach seems to be inadequate.[1]

In 1990, a protocol (DH-II-90) with reduced chemotherapy and radiotherapy doses was developed in our institution in an attempt to reduce the major toxic effects, but still following existent precepts in the treatment of pediatric LH: combined therapy adapted for the risk group. Here the results of our experience are presented.

The objectives of this study were: 1) To assess the overall survival (OS) and event-free survival (EFS) of HL children treated with the DH-II-90 protocol, 2) to identify clinical and therapeutic strategies that impact on EFS of this group of patients.

Methods

From January 1990 to December 2005, with the approval of the Research Ethics Committee of the institution, 68 children and adolescents with naive LH were treated using the II-DH-90 protocol which consists of combined chemotherapy and radiotherapy adapted for the risk group. All patients had pathological confirmation of the diagnosis. Assessment of extent of disease included computed tomography, chest x-rays, neck and abdomen ultrasound exams, bone marrow biopsy, (1) myelogram, (2) gallium scintigraphy and the erythrocyte sedimentation rate.

Dosing regimen: patients with stage IA and IIA (low risk) received three cycles of ABVD (adriamycin 25 mg/m^2/dose on days 1 and 15, bleomycin 10 mg/m^2/dose on days 1 and 15, vinblastine 6 mg/m^2/dose on days 1 and 15 and dacarbazine 250 mg/m^2/dose on days 1 and 15) and involved-field radiotherapy at doses of from 1800 to 2100 cGy. The infradiaphragmatic region to the bifurcation of the aorta was irradiated including the spleen for mediastinal presentations. Patients in stages IIIA, IVA and those with B symptoms (high risk) received three cycles of ABVD as well as three cycles of MOP (onco-cloramin - mechlorethamine hydrochloride - 5 mg/m^2/dose on days 1 and 8, vincristine 1.5 mg/m^2/dose on days 1 and 8 and prednisone 40 mg/m^2/day for 14 days). This was later replaced by COP, in which onco-cloramin was exchanged for cyclophosphamide 600 mg/m^2/dose due to supply difficulties. Radiotherapy for stage IIIA was similar to that applied to stages I and IIA. In stage IV and B subgroups, radiotherapy was extended, involving the supra- and infradiaphragmatic fields with ovarian protection when necessary.

For descriptive analysis the mean, standard deviation, minimum, median and maximum were calculated for continuous variables (age and radiotherapy dose). Frequencies and percentages were calculated for non-continuous variables (gender, bulky disease, mediastinal mass, B symptoms, histology, stage, radiation dose greater than or less than 2100 cGy, induction failure, relapse, death and second malignancy). Survival curves were constructed using the Kaplan-Meier method with patients stratified by staging (high risk and low risk). The curves were compared according to stage, age, presence of bulky disease, mediastinal mass, radiotherapy (involved field and extended field), dose of radiotherapy (< 2100 and > 2100 cGy) and B symptoms (yes or no). Cox regression was used to investigate the effect of age, presence of bulky disease, mediastinal mass, radiotherapy (involved field and extended field) and dosage of radiotherapy (< 2100 and > 2100 cGy), presence of B symptoms (yes or no) on event-free survival. A level of significance of 5% (p-value < 0.05) was used.

Definitions

- Event-free survival (EFS): calculated from the date of diagnosis to the date of the event, the date of last visit or June 30, 2008.
- Overall survival (OS) was considered the interval between diagnosis and date of death.
- Events: death from any cause, induction failure, relapse and second malignancy.
- Complete remission: a patient without clinical or radiological evidence of Hodgkin's disease (HD).
- Progressive disease: An increase of 25% or more in the size of at least one measurable lesion or the appearance of a new lesion or recurrence of B symptoms.
- Induction failure: partial response or progressive disease at the end of chemotherapy or radiotherapy.
- Bulky disease: lymph node or cluster of lymph nodes larger than 10 cm or mediastinal masses with sizes larger than 1/3 of chest diameter in the region of the 5th to 6th thoracic vertebrae.

Results

Of the 68 patients enrolled in this study, 20 were female and 48 male. The median age was 9 years old, ranging from 2 to 21 years. The most frequently involved ganglia were the cervical (86.8%) followed by supraclavicular (48.5%), mediastinal (39.7%), diaphragmatic (33.8%), axillary (14.7%) and inguinal chains (10.3%). The number of involved lymph nodes was less than three in 63.2% and over six in 11.7% of cases.

Twenty-seven (41.5%) patients had large tumors classified as bulky disease [11 (18%) mediastinal and 16 (23.5%) cervical]. The staging was as follows: nine (13.2%) stage IA, 29 (42.6%) IIA, five (7.4%) IIB, nine (13.2%) III, ten (14.7%) IIIB; two (2.9%) IV and four (5.9%) IVB. Histologic evaluations identified 62 patients (91.2%) with classical HL and four (5.9%) with nodular lymphocyte-predominant HL. Two patients (2.9%) had a diagnosis of Hodgkin and Reed-Sternberg cells, however classification was not possible. Among the cases of classical HL, 39

(57.4%) were classified as mixed cellularity, 18 (26.5%) as nodular sclerosis and five (7.4%) as lymphocyte depletion. There were no cases of classical lymphocyte-rich HL. Table 1 summarizes the main characteristics of this population.

Table 1. Clinical and laboratory characteristics of patients with Hodgkin's lymphoma treated with the DH-II-90 protocol

Variable	Total (%)
Age (years)	
< 5	16 (23.5%)
6 - 10	26 (38.2%)
11 - 15	22 (32.4%)
≥ 16	4 (5.9%)
Histology	
Mixed cellularity	39 (57.3%)
Nodular sclerosis	18 (26.5%)
Lymphocyte depletiona	5 (7.4%)
ymphocyte-predominant	4 (5.9%)
Not classified	2 (2.9%)
Staging	
IA	9 (13.2%)
IIA	29 (42.6%)
IIB	5 (7.4%)
IIIA	9 (13.2%)
IIIB	10 (14.8%)
IVA	2 (2.9%)
IVB	4 (5.9%)
Risk classification	
Low risk	38 (55.9%)
High risk	30 (44.1%)
Radiotherapy	
Involved field	28 (41.2%)
Involved field	40 (58.8%)
Total dose of radiotherapy - band (in cGy)	
< 2100	24 (35.3%)
> 2100	44 (64.7%)

Note: Data collected from medical records of patients treated between 1990 and 2005

All patients received three cycles of ABVD. High-risk patients received additional chemotherapy as described in the protocol; MOP was administered in 18 patients (60%) and COP in 12 patients (40%). Twenty-eight patients (41.2%) received involved-field irradiation and 40 (58.5%) extended-field radiotherapy with the mean total dose being 2736 cGy; 64.7% were submitted to doses higher than 2100 cGy.

Forty-one patients (61.2%) did not present with any acute complications related to chemotherapy. Easy-to-control infection was reported in 23 cases (33.8%). No fatal acute toxicity related to treatment was observed. The follow-up off therapy ranged from 22 to 207 months with an average of 109.5 months.

Complete remission

The overall complete remission rate after chemotherapy anticipated by the protocol was 94.1% (64/68). For low risk patients, who received three cycles of ABVD, the complete remission rate was 97.3% (37/38), and for high risk patients, who received three cycles of COP or MOP, it was of 90% (27/30). Four patients (5.9%), all of whom were over 5 years old, suffered induction failure; three were rescued using alternative treatments and one died of the disease.

Event-free survival and overall survival

The probability of event-free survival at five years was 92.1% ± 4.4% for low-risk patients *versus* 86.5% ± 6.3% for high-risk patients (Figure 1), but there is no statistically significant difference (p = 0.969) between the curves at ten years (88.9% ± 5.2% *versus* 86.5 ± 6.3).

Table 2 shows that on comparing the different age groups (p = 0.577), bulky disease (p = 0.341) or involved-field *versus* extended-field radiotherapy (p = 0.733), the probabilities of EFS were not statistically different (Figure 1). The probability of EFS in the first five years after treatment was better for patients without B symptoms (91.8 ± 3.9% *versus* 84.2% ± 8.4 for patients without and with B symptoms, respectively; p = 0.014), but the curves are similar at ten years of follow up (89.2% ± 4.6% *versus* 84.2% ± 8.4%).

The greatest difference was observed on comparing the presence or absence of mediastinal mass and radiation dose (greater than or less than 2100 cGy). Patients with mediastinal masses had EFS of 75.0% ± 12.5% and 65.6% ± 14.0%, and patients without mediastinal masses had EFS of 92.8% ± 3.4% and 92.8% ± 3.4%, respectively at five and ten years, respectively (p-value = 0.020).

Table 2. Probability of event-free survival at 10 years for children and adolescents with Hodgkin's lymphoma, according to the clinical characteristics and radiation therapy

	EFS at 10 years % ± SD	p - value
Age (years)		
< 5	90.0% ± 9.8	
> 6 and < 10	84.6% ± 7.1	0.577
> 10	82.9% ± 7.9	
Bulky disease		
yes	89.7% ± 4,8	0.341
no	76.9% ± 9,6	
Radiation		
Involved-field	89.1% ± 5.9	0.733
Extended-field	83.0% ± 6.5	
B Symptoms		
yes	89.2% ± 4.6	0.710
no	84.2% ± 8.4	
mediastinal mass		
yes	65.6% ± 14.0	0.020
no	92.8% ± 3.4	
Irradiation		
< 2100 cGy	100%	0.014
> 2100 cGy	81.0% ± 6.1	

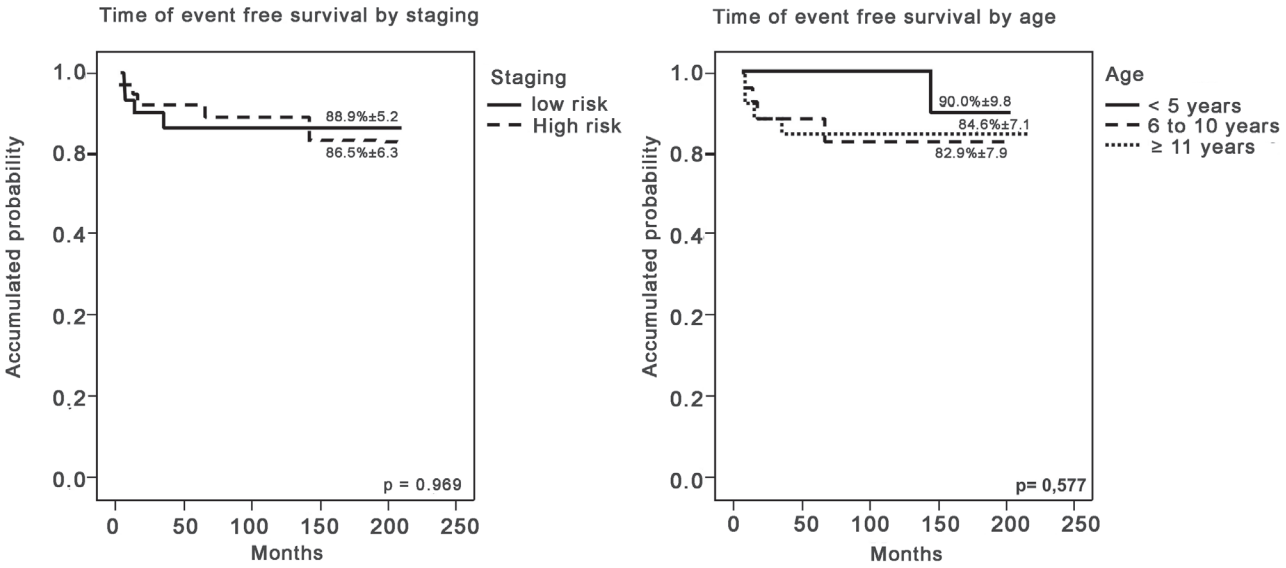

Figure 1 - Estimated event-free survival for patients with Hodgkin's lymphoma by staging and age group using the Kaplan-Meier method

Patients who received low-dose radiotherapy had 100% of EFS and those who received doses of more than 2100 cGy had EFS of 84.0% ± 5.5% and 81.0% ± 6.1% at five and ten years, respectively (p-value = 0.014).

One low-risk and two high-risk patients relapsed (4.4%). The case of relapse in the low-risk group (nodular sclerosis - histological variant) was submitted to several attempts of salvage therapy, including autologous and one allogeneic bone marrow transplantation, but died from complications of the latter. The two cases in the high-risk group attained remission after alternative chemotherapy, but both have descriptions of late effects of treatment: one with structural change of the thyroid gland and changed semen analysis. Thus, there were three deaths (4.4%), two from refractory disease and one from complications of allogeneic bone marrow transplantation.

The overall survival (Figure 2) was 96.1% ± 3.8% for the low-risk group and 93.3% ± 4.5% for high-risk patients at ten years (p = 0.402).

Of the surviving patients, 35/65 (53.8%) had some type of late toxicity. Among them, 15 (42.9%) suffered thyroid gland dysfunction (six with functional dysfunction, four with hypothyroidism and four with hyperthyroidism), nine (25.7%) had benign tumors and two (2.9%) thyroid carcinoma. The latter two had been submitted to local radiotherapy at 5 and 8 years old with doses greater than 2100 cGy.

An analysis of the survival of high-risk patients was also performed comparing the use of MOP and COP. However no significant differences in OS (p = 0.821) or EFS (94.1% and 75% respectively, p = 0.135) were identified.

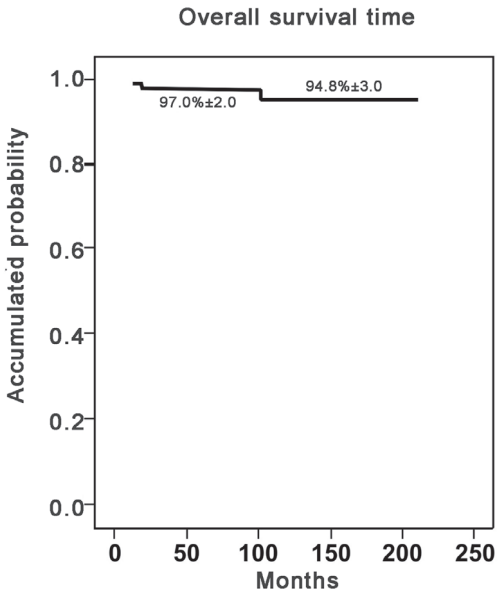

Figure 2. Kaplan-Meier survival curve for the entire group of patients with Hodgkin's disease

In the multivariate analysis, no variable was identified that impacted on the occurrence of induction failure, relapse, second malignancy or death.

Discussion

The DH-II-90 protocol proposed a reduction in the intensity of chemotherapy and radiotherapy; all patients completed the entire recommended program with low acute toxicity.

The prevalence of the disease in under 10-year-old children in our study, which is not common to other authors, calls the attention.[2,3]

There was a predominance of the mixed cellularity subtype (57.4%) consistent with the pattern in developing countries, although in Brazil this is controversial.[3-5]

In this study, the complete remission rate after chemotherapy was projected at 94.1%. OS of 97.0% ± 2.0 and 94.9 ± 3.0%, and EFS of 89.7% ± 3.7% and 87.9 ± 4.0 were observed, respectively at five years and ten years for the entire group of patients. These results are similar to those described in the literature.[6-9] Probabilities of OS and EFS were not statistically different when separated by staging as low or high risk (p = 0.402 and 0.969, respectively). This may be explained by the small sample size and because small variations in field strength and dose of radiotherapy treatment occurred as it was not adequately standardized, which may have interfered in the evaluation of EFS.

Recently, several treatment protocols have also tried to reproduce the excellent results achieved with the combined treatment, but with reductions in the number of cycles of chemotherapy and dose and field in radiotherapy.

The Nazionale Tumori Istittuto group[10] reported long-term results equivalent to previous therapies with a randomized trial that used four cycles of ABVD and involved-field radiotherapy at 3000-4000 cGy compared with ABVD and extended-field radiotherapy. The probabilities of EFS and OS were 93% and 96% for patients who underwent extended-field and 94% and 94% for involved-field radiotherapy, respectively. With the exception of pulmonary toxicity, the ABVD combination seemed to be less toxic than traditional regimens with alkylating agents - nitrogen mustard and procarbazine.

Moreover, the German Hodgkin's lymphoma Study Group (GHLSG) reported the results of the H10 trial which randomized patients with early-stage Hodgkin's disease to receive two or four cycles of ABVD, with a second randomization of involved-field radiotherapy at doses of either 3000 or 2000 cGy. The results showed similar survival between the groups, but with greater toxicity in patients who were submitted to more courses of chemotherapy and higher doses of radiotherapy as cited by Strauss.[11]

Donaldson et al. tested the combination of vincristine, doxorubicin, methotrexate, and prednisone (VAMP) to treat children and adolescents with HL.[12] After four cycles of the combination with low dose involved-field radiotherapy (1500 cGy for those with complete response and 2500 cGy for those with partial response), the results were effective for the low-risk early stage group with OS and EFS probabilities of 99% and 93%, respectively. The advantage of this protocol was that it avoided the use of alkylating agents, such as bleomycin and etoposide and high-dose or extended-field radiotherapy.

For high-risk patients, the DH-II-90 protocol added three cycles of MOP, which was later changed to three cycles of COP as onco-cloramin was no longer available on the market. On separating COP and MOP, an evaluation of the probability curves for OS and EFS were not statistically different (p = 0.821 and p = 0.135, respectively).

Although no significant difference was identified, the probability of EFS was worse when using the COP regimen as additional chemotherapy (75% *versus* 94.4%) was used and there were two induction failures and one relapse in this group compared with only one induction failure in the MOP group. Both groups had one death each due to refractory disease. The use of COP with prednisone in the treatment of HD has not previously been described. Hudson et al. evaluated the use of COP with procarbazine in combination with VAMP for high-risk patients but the results were unsatisfactory.[6]

Another scheme tested by Friedman et al.[13] was the use of VEPA (vinblastine, etoposide, prednisone and doxorubicin) in combination with involved-field radiotherapy for advanced-disease patients (stage III or IV) and those with unfavorable risk factors and bulky tumors. The probabilities of OS and EFS at five years were 81.9% and 67.8%, respectively, with rates even lower for patients with advanced illness.

A study by Kelly et al. investigated whether treatment response could be improved with the use of intensive chemotherapy, that is, four cycles of BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone). Those with a quick response should receive consolidation treatment with four cycles of COPP/ABV for girls and ABVD for boys, to try to reduce late effects on fertility in males. The study has a very short follow-up, but showed that 72% of patients responded rapidly and only one had relapsed within six months of follow up. The use of BEACOPP causes acute toxic effects on bone marrow and also there is a higher late toxicity, with the risk of secondary leukemia, infertility, and heart and lung toxicity.[14]

The treatment of advanced stage HL is still under discussion, with ABVD with or without MOPP still used in many countries.[15]

The DH-II-90 protocol recommends the use of low-dose involved-field radiotherapy for early-stage HL and extended-field radiotherapy for stage IV patients and those with B symptoms. The probability of EFS was higher with the use of low-dose radiotherapy (Table 2; p = 0.014), as has been reported by other groups. (16) The probability of EFS was also significantly higher without any mediastinal mass (Table 2; p = 0.020) probably because of the smaller irradiated field as, with mediastinal involvement, the infradiaphragmatic region up to the aortic bifurcation is irradiated, and normally a higher dose of radiotherapy is used.

The Pierre et Marie Curie study group[17] showed that classical blanket irradiation can be replaced by fields limited to the site previously involved by the disease - involved-field radiation, believing that chemotherapy will adequately

treat the microscopic disease of macroscopically uninvolved areas. These findings were later confirmed by other authors[10,18,19] and the combined modality of chemotherapy plus involved-field radiotherapy has become the gold-standard treatment for low-risk HL, even for those with unfavorable risk factors. Some groups[20,21] began to defend the use of chemotherapy alone to treat HD, especially for patients with localized disease, arguing that: 1) treatment with this pure modality can be used in developing countries where there is no equipment or trained personnel for appropriate irradiation; 2) precise surgical or clinical staging would not be essential; 3) late complications in growth and second malignancy associated with radiotherapy would be avoided. On the other hand, the disadvantages are exposure to high doses of alkylating agents and morbidity related to myelosuppression, infertility and secondary leukemia.[10] The evaluation of protocols for HD treatment with chemotherapy alone has been difficult because most reports are described in nonrandomized cohort studies with a limited number of patients, where samples were not properly controlled and, often, those with unfavorable risk factors were excluded.[9,22] This conduct does not seem appropriate for cases of bulky disease, there are few long-term evaluations of toxicity in protocols and, in cases of relapse, the child would receive even more drugs and radiotherapy resulting in increased toxicity.[23]

A study conducted in India by Laskar et al.[8] confirmed the need for the use of radiotherapy as consolidation treatment for HD. In this study, HL patients were randomized to receive six cycles of ABVD alone or in combination with radiotherapy. The probability of EFS and survival at eight years of follow-up were 76% and 89% for the group on chemotherapy alone and 88% and 100% for the group receiving combined treatment, respectively. On evaluating the under 15-year-old patients alone, this difference was even greater (EFS at eight years was 53% for the chemotherapy alone arm and 97% for the combined modality, $p = 0.02$).

The Children's Cancer Group (CCG) also tested the use of radiotherapy as consolidation treatment for those patients who achieved complete remission after combination chemotherapy, randomizing them to receive low-dose involved-field radiotherapy or no other treatment.[24] This study had to be stopped due to the large number of relapses in the chemotherapy alone group. Estimates of OS for the randomized groups are not different due to the success of salvage treatment, including radiotherapy.

The German study, GPOH-HD-95, also evaluated the omission of radiotherapy for patients who achieved complete response to chemotherapy as cited by Hudson et al.[23,25] The probability of EFS at five years for low-risk patients (stages IA and IIA) was 97% and 94% respectively for those treated with chemotherapy alone and in combination with radiotherapy. However, for intermediate- and high-risk patients the probability of EFS was significantly lower without radiotherapy (79% vs. 91%). Again, the OS was not different, indicating that these patients can achieve a second remission with salvage treatment.

The rationale for the use of combined therapy is that while chemotherapy takes care of subclinical disease spread, radiotherapy is necessary for local control of persistent tumor. The combination also allows you to limit the intensity and duration of chemotherapy and the irradiation dose and hence the associated late effects. The benefits of radiotherapy in controlling the disease, therefore, still appear to be greater than the potential adverse effects, especially in patients with bulky, advanced stage or refractory disease.

Acute adverse effects related to treatment were easy-to-treat. This suggests that this is a safe treatment, with a low complication rate, particularly for outpatients. Patients who received additional chemotherapy using COP or MOP protocols had higher rates of hospitalization (46.1%) compared with the group that only used ABVD (28.6%), but this finding was expected, since they were exposed to greater number of chemotherapy cycles.

Another important advantage of ABVD was the low incidence of late toxicity compared with regimens containing alkylating agents. MOPP, for example, induces infertility in most over 30-year-old men and women due to the procarbazine. Testicular dysfunction is dose dependent and is also seen in patients treated with OPPA or OPPA/COPP regimens. In addition, patients treated with onco-cloramin have a 3% risk of presenting with acute leukemia during their lifetimes.[26] The ABVD protocol has few acute effects and also has less potential for leukemogenesis and infertility. It is associated however, with a high risk of chronic cardiomyopathy and pulmonary dysfunction, especially in children, but the severity and frequency of these effects are related to cumulative dose (usually after six to eight cycles) and partly to its association with radiotherapy. ABVD is therefore accepted as the gold standard for treatment of HL in combined modality regimens for low-risk patients and should be tested with all other new drug combinations.[7]

By applying only three cycles of ABVD in these patients, there is also a significant reduction in late effects related to treatment, limiting the cumulative dose and thus lower resulting heart and lung toxicity. The cumulative dose of 150 mg/m^2 of doxorubicin is safe, however doses greater than 300 mg/m^2 are associated with higher incidences of congestive heart failure.

The DH-II-90 protocol does not use procarbazine, hence the long-term toxicity rate, especially related to fertility is lower. Moreover, despite the use of onco-cloramin for most patients (26.4%), which was subsequently replaced by cyclophosphamide because onco-cloramin disappeared from the Brazilian market, there were no cases of secondary leukemia or myelodysplasia, even after a long follow-up period (average follow-up among patients who received this

drug was 12.47 years with one patient excluded due to death by refractory disease after 14 months). Moreover, the incidence of secondary leukemia also appears to have been reduced with the abandonment of splenectomy, which is considered by some authors as an independent risk factor.

Sequelae related to the thyroid include hypothyroidism, hyperthyroidism and benign and malignant thyroid nodules. A retrospective multicenter study of the Childhood Cancer Survival Study Group reported thyroid abnormalities in 34% of 1791 HD survivors.[27] Risk factors for hypothyroidism include low age during treatment and high doses of irradiation. Despite this, over one third of patients with abnormal TSH presented spontaneous improvement. Thyroid nodules occur later, at an average of 14 years of follow-up, and the risk of cancer is from 1.74 to 36.4 times higher than in the general population. In the DH-II-90 study, 42.9% of patients had some dysfunction of the thyroid gland and two cases had carcinoma both of whom had been irradiated with doses greater than 2100 cGy and were younger than 10 years old.

No cases of secondary breast cancer were reported however, this study has a mean follow-up of 10.4 years, which is short to evaluate this type of toxicity, as the risk increases dramatically from ten years of follow-up with the cumulative incidence, at age 40 years, being 12.9%.[28]

In the present study, the mean follow up of patients off therapy was 109.5 months (9.1 years) and therefore this type of toxicity could not be evaluated. Whether the DH-II-90 protocol has in fact reduced the incidence of secondary neoplasms by reducing the chemotherapy and radiotherapy is a question to be answered in the future after a longer follow-up of these patients.

This remains the biggest challenge for caregivers of patients with HL; maintaining the cure rates with minimal toxicity. It is worth remembering that the desire to provide a better quality of life for these patients should begin with the choice of treatment not only the team that supports them in the outpatients' clinic off therapy. The interaction between clinical oncologists, pathologists, radiologists and radiation oncologists is essential to better address this need. In future programs, children with localized disease and lymphocyte-depleted type histology may only need to be submitted to surgical treatment. Children with bulky disease, particularly those with a mediastinal mass, should be considered to receive an intensified chemotherapy protocol.

Conclusions

The DH-II-90 protocol applied to children and adolescents with HL resulted in satisfactory OS and EFS rates and good tolerance of treatment. Based on these data, it is clear that restricted ABVD cycles associated with low-dose involved-field radiotherapy were sufficient for the long-term control of HL in low-risk patients with low morbidity rates including late complications. For high-risk patients, the DH-II-90 protocol was also effective but with greater acute and late toxicity. The use of COP appears to be as efficient as MOP despite the shorter follow-up of patients using this combination. Thyroid abnormalities were the most common sequelae in this group of patients, with two cases of thyroid carcinoma. This will require a review of radiotherapy in future studies. The presence of mediastinal masses had a negative impact on EFS, which should also be considered when developing future studies.

Resumo

O desafio do tratamento do linfoma de Hodgkin na infância reside na redução da toxicidade aguda e tardia sem afetar os bons resultados terapêuticos. Crianças e adolescentes portadores de linfoma de Hodgkin recém-diagnosticado foram tratados com o protocolo institucional DH-II-90. Os objetivo deste trabalho foram: 1)avaliar as taxas de sobrevida global (SG) e livre de eventos (SLE) do protocolo DH-II-90 aplicado a portadores de LH; 2)avaliar as taxas de SG e SLE conforme estádio, idade, tumor "bulky", massa mediastinal, sintomas B, dose de radioterapia e 3)descrever os efeitos tardios. Sessenta e oito pacientes portadores de LH recém-diagnosticado, com idade entre 0 e 21 anos (idade mediana 9 anos, 20F:48M), foram tratados com quimioterapia (baixo risco:ABVD; alto risco:ABVD+MOP/COP) e radioterapia. O estadiamento foi distribuído desta forma: nove (13,2%) estádio I A; 29 (42,6%) II A; cinco (7,4%) II B; nove (13,2%) III A; dez (14,7%) III B; dois (2,9%) IV A e quatro (5,9%) IV B. A SG em dez anos foi de 96,1% ± 3,8 para o grupo de baixo risco e 93,3% ± 4,5 para o de alto risco (p:0,402). A SLE foi de 88,9% ± 5,2 em dez anos para o de alto risco e 86,5% ± 6,3 para o de baixo risco (p: 0,969). A presença de massa mediastinal e doses de radioterapia maiores que 2100 cGy (p= 0,020 e p= 0,014, respectivamente) apresentam impacto negativo na SLE e a doença estádio I tem impacto positivo na SLE. Disfunção e carcinoma de tireoide são os efeitos tardios mais frequentes neste grupo de doentes. O protocolo DH-II-90 obteve resultados terapêuticos favoráveis, porém as taxas de complicações tardias, embora aceitáveis, demandam revisão do programa terapêutico. Rev. Bras. Hematol. Hemoter. 2010;32(4):295-302.

Palavras-chave: *Linfoma de Hodgkin; criança; quimioterapia; radioterapia; sobrevivência.*

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