Review

Present and future strategies of treatment in childhood Hodgkin's lymphomas

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Summary

With the dramatic improvement of therapeutic results in Hodgkin's disease patients, challenges still remain in identifying the minority of patients with a poor prognosis who need intensive therapy and in reducing the costs of therapy in the successful outcome of the disease in children as in adults. It has been progressively recognized that therapeutic problems of children are similar to those of adult patients. However, the late effects of staging splenectomy and of radiotherapy on growing patients are more severe in children and the most serious sequelae is that of developing a second malignancy in patients who will have a very long life span. Ways of decreasing the long-term effects of therapy have been different in adults and children. The wide use of efficient chemotherapy has allowed omission of staging laparotomy, and reduction of the fields and doses of radiation. Compared to treatment with chemotherapy alone, which requires high cumulative doses of drugs with a potential toxicity, combined modality therapy has emerged as the best treatment for children, with low-dose and limited-volume irradiation, short chemotherapy and without the administration of alkylating agents and anthracyclines in selected groups of patients.

Key words: childhood, Hodgkin's disease, treatment

Introduction

The use of radiotherapy given at high doses (ranging from 40 to 44 Gy) has made Hodgkin's disease no longer a fatal disease. The extension of the radiation fields guided by systematic surgical staging yielded the cure of a significant number of patients, adults as well as children. The first pediatric published series reported a 57% relapse-free survival and a 92% survival for 52 children staged IB–IIIB from 1969 to 1977 [1]. The introduction of chemotherapy like MOPP achieved dramatic results in advanced disease otherwise not curable [2]. During that time, the children were considered and treated as young adults and the major aim was to increase the survival rate.

However, with the increasing number of cured patients and longer follow-up, the late effects of staging laparotomy and of treatment have been specified. The late effects of chemotherapy, such as increased incidence of acute leukemia or male sterility are common to adults and children. However, some of the late consequences of radiation therapy tend to affect children more significantly than adults, with an inverse relationship to age at the time of treatment. The side effects are clearly related to the radiation dose, fields and fractionation, and to the age of the child at time of treatment. Thyroid dysfunction and growth impairment are the most frequent consequences [3], but other late consequences can be life-threatening, such as pericardial effusion, coronary artery stenosis and pleural effusion, which may occur many years after treatment [4]. The successfully treated patients have a very long life-span, but the risk of developing a second solid tumor increases with time elapsed since treatment. A report of 1380 pediatric patients treated for HD between 1955 and 1986 revealed that the probability of developing a second tumor is 6% at 15 years, but does not reach a plateau even after 25 years, whereas leukemias reached a plateau after 15 years. In the same series, 14 female patients developed breast cancer. The estimated probability of developing breast cancer was 32% at 40 years of age, underscoring the need of appropriate surveillance and screening of this very high-risk population [5].

So, for the last 15 years, knowledge of the late effects of both chemotherapy and radiotherapy on children have been arguments in favor of the use of a single modality, avoiding the other one to minimize the toxicity of the treatment. I will summarize these different approaches and the advantages of a combined modality.

The use of radiation therapy alone

With respect to adults, in whom late effects linked to growth do not exist, there is still a long debate on the use of radiation therapy alone or combined with chemotherapy in favorable cases. It has been shown in adults that several criteria are indications for combined modality treatment: massive mediastinal mass, B symptoms, three or more lymph node areas involved by...
Hodgkin's lymphoma, infra-diaphragmatic disease, high erythrocyte sedimentation rate and mixedcellularity or lymphocytic depleted subtype. Radiation therapy alone may be used in only 10% to 15% of the patients. However, in this subgroup of patients, laparotomy and splenectomy with their risk should be included in the staging procedure to delineate the radiation fields. All these factors are reasons for long debate, even with respect to adults, and so far, 22 randomized trials of radiotherapy versus chemotherapy plus combination chemotherapy have been carried out world-wide without being able to establish a definitive superiority of one approach over the other [6].

The use of chemotherapy alone

Once the effectiveness of chemotherapy had been proven, the following question was the possibility to cure children without the use of radiation. The rationale of most protocols based on chemotherapy alone always refers to the experience of Olweny in Uganda where radiation machines were not available. Despite the lack of these machines, in a series of 48 children who received 6 cycles of MOPP, actuarial survival in stage I and II was 75% and 60% in stages III and IV [7].

With this background, several teams chose the policy of chemotherapy alone. According to the stage, in Australia children with stage I and II received from 6 courses of MOPP and children with more advanced disease received from 6 to 12 courses [8]. In the United Kingdom and in Amsterdam, patients without large mediastinal mass or without lymph node swellings (<4 cm) received 6 cycles of MOPP or CHVPP without additional radiotherapy [9,10].

In all these studies, children received at least 4 cycles and most of the time 6 cycles or more of chemotherapy that contained alkylating agents and procarbazine. In our paediatric experience, in adults, 6 MOPP induce sterility in more than 90% of the boys, as well as an increased risk of secondary leukemia that we consider unjustifiable.

The number of patients included in these previously mentioned studies were not sufficient for randomized trial. The Pediatric Oncology Group addressed the question of the effectiveness of chemotherapy alone versus chemotherapy combined with radiation therapy in a randomised study in advanced stage. Children with stages IIb, IIIA2, IIIB and IV were treated with 4 cycles MOPP + 4 cycles of ABVD with or without 21 Grays total or subtotal nodal irradiation. The event-free survivals of the two regimens were not statistically different (78.4% without additional radiation therapy and 78.2% with radiation therapy). The survivals were similar in both groups (94% and 88%, respectively) [11].

The Children Cancer Study Group conducted a randomised study in stages III and IV. It compared MOPP alternating with ABVD for 12 months to ABVD for 6 months followed by 21 Grays. At 2 years, the event-free survivals of the two regimens were similar (84.8% and 88.5%) [12].

It could therefore be concluded that the addition of chemotherapy does not offer any significant advantage over chemotherapy alone. However, in these studies children treated without radiation therapy received 6, 8 and 12 cycles of chemotherapy alternating MOPP and ABVD. This chemotherapy has a toxicity which is now well known. We mentioned previously the risks of 6 cycles of MOPP. Six cycles of ABVD leads to a high cumulative dose of adriamycin: 300 mg/m² and a high cumulative dose of bleomycin 120 mg/m². This dose explains the very high pulmonary toxicity reported in the CCSG experience with one fatality. These results should prevent giving so many courses of ABVD when combined with radiation therapy to the mediastinum [12].

The knowledge of late consequences of splenectomy, of high-dose radiation therapy and of high cumulative doses of chemotherapy supported the wide use of combined modality therapy to treat childhood Hodgkin's disease. In this way it appeared possible to gradually decrease both radiation therapy and chemotherapy.

The use of combined modality treatment

The use of chemotherapy allowed a reduction of the fields and doses of radiation therapy. On the other hand, the use of radiation therapy allowed the reduction of the duration of chemotherapy and the use of other combinations than MOPP.

The reduction of radiation fields

The Hodgkin's disease Intergroup for childhood Hodgkin's disease performed a randomised 3-arm study in pathologically staged children. This compared involved radiotherapy alone, extended field radiotherapy and involved field radiation given with 6 MOPP.

There was no significant difference in survival: however, disease-free survival in the MOPP arm was excellent (93%), contrasting with the results of the other 2 arms, which were 41% and 67%, respectively. This result shows that when radiation therapy is used along with chemotherapy, fields of radiation therapy can be limited to involved areas [13].

The first paediatric study carried out at Institute Gustave Roussy involved 60 children clinically staged. They were treated by involved field radiation after chemotherapy by MOPP. Their disease-free survival was 86% with only 2 relapses outside an irradiated area [14]. The Polish pediatric group obtained similar good results in treating patients with involved field radiotherapy after MOPP or B-DOPA [15].

The term 'involved field' should be defined accurately in each study since the definition of an involved field...
may vary from one institution to another one or from one group to another one. Some investigators prefer to use the anatomic definition of separate lymph node regions adapted for staging purposes at the Rye symposium. Some groups recommend irradiating simply the clinically involved nodal areas, without taking into consideration staging definitions.

**The reduction of radiation doses**

The reduction of radiation doses was pioneered by the Stanford group. After systematic splenectomy, 55 children were given 6 MOPP. Radiation doses (ranging from 15 to 25 Grays) were decided according to the age and response to treatment, with boosts often being added [16]. In the Toronto study, radiation was given in extended fields with 6 MOPP chemotherapy. Both these series had the same excellent results as those of the previous studies using high-dose radiotherapy with survival higher than 90% [17].

Other studies confirmed the efficacy of such doses on larger groups of patients, at a national level. In the first French study, the radiation dose was tailored to the response to primary chemotherapy. At completion of chemotherapy, patients who had achieved good response (at least 70% regression of initial measurable disease) were given 20 Grays. Only 5% of the patients who did not achieve this good response were given 40 Grays. The updated results show that at 5 years, overall survival and disease-free survivals are 93% and 86%, respectively [18]. In the first Italian study, the radiation dose was 20 or 25 Grays (according to the age of the patient) [19]. In the German studies, the radiation doses depended on the duration of the previous chemotherapy: 35 Grays in stages I–IIA after 2 cycles, 30 Grays in stages II–IIIA after 4 cycles and 25 Grays after 6 cycles [20]. The good results of all these studies demonstrate clearly that radiotherapy at a dose of 20 Grays can be safely used to cure patients after effective primary chemotherapy.

The follow-up of most of the cohorts of patients treated with low-dose radiation is not long enough to evaluate the definite effects of such doses. However, the experience of children who have been given 20 Grays at a younger age for a malignancy other than Hodgkin’s disease (for instance for a Wilms’ tumour) suggests that patients with Hodgkin’s disease who received such a dose will have no or mild late effects, which are not comparable to those observed after 40 Grays.

**The reduction of chemotherapy duration**

To minimise the risk of sterility and secondary acute leukemias induced by alkylating agents and procarbazine, the next goal was to reduce exposure to MOPP. The first way of doing so, was to reduce the number of cycles. In a randomised study conducted in France, adult patients with stage I and II were given 3 or 6 MOPP. The results of surgical restaging laparotomy after MOPP and the disease-free survival were similar in both arms [21]. The study performed in children in Villejuif confirmed that 6 cycles of MOPP are not more effective than 3 cycles, reducing the cumulative doses of mechlorethamine and procarbazine [14].

**The use of other chemotherapy than MOPP**

The second way chosen to reduce the toxicity of chemotherapy was to use drugs which are less toxic than those contained in MOPP. ABVD combination became the challenger of MOPP. Once it was convincingly shown that this combination was effective in the patients who had failed MOPP, alternating cycles of these 2 programs (MOPP and ABVD) turned out to be the best effective regimen in advanced disease and clearly superior to MOPP alone [22]. In adults, the Milan team, and subsequently the Cancer and Leukemia Group B and the EORTC group addressed the question of efficacy of ABVD alone versus alternating courses of MOPP + ABVD in advanced stages. They concluded that ABVD was as effective as the alternating regimen [22, 23]. The only randomised study conducted in children was the first French National study that showed that 4 ABVD were equivalent to 2 MOPP + 2 ABVD in localised stages [18].

Several other paediatric teams confirmed the efficacy of ABVD alone combined with low-dose radiotherapy in non-random studies. (The National Italian Group, the Milan paediatric team and the Children Cancer Study Group) [19, 24, 12].

ABVD was found to be an interesting alternative to MOPP since it is devoid of alkylating agents and procarbazine. However, it contains drugs which are known to be potential inducers of lung damage or cardiomyopathy [25].

This explains why some groups have investigated other combination chemotherapy than MOPP or AVBD, trying to eliminate mechlorethamine as well as adriamycin from the chemotherapy.

Up to 1985, the chemotherapy used by the German paediatric group consisted of OPPA (vincristine, prednisone, procarbazine at the same doses as in MOPP, combined with adriamycin: 40 mg/m² twice) and COPP (cycles similar to MOPP but with cyclophosphamide instead of the mustard). In 1985, the same group began a study to eliminate procarbazine from the chemotherapy. OPPA became OPA, and methotrexate replaced procarbazine in the COPP combination, resulting in the COMP regimen. In advanced stages, progressions and relapses were significantly higher than in the preceding protocol and the study was prematurely stopped, arguing for the need for an effective drug to replace procarbazine [26].

Very few drugs are both non-toxic (or with acceptable toxicity), and active in Hodgkin’s disease. Preliminary data indicated that etoposide might have a role to play and this drug has been included in paediatric studies. For instance, OPPA became OEPA in the
German HD90 [27], the Memphis team added VP 16 to vinblastin and adriamycin for advanced stages [28]. In 1990, the French national group initiated a new study for stage I and II disease, based on the 'VBVP' combination. This consists of etoposide 100 mg/m² for 5 days, bleomycin 10 mg/m² day 1, vinblastin 6 mg/m² days 1 and 8, prednisone 40 mg/m² for 7 days. All patients with clinical stages I and II are given 4 cycles of 'VBVP' at 3-week intervals. The subsequent treatment is adapted to the response to chemotherapy. Patients who exhibit a good response after 4 cycles are given 20 Grays additional radiation therapy. Patients who do not achieve such a good response are given 2 cycles of OPPA chemotherapy as previously described. The response to these last 2 cycles determined the dose of radiation therapy: 20 Grays for good responders and 40 Grays for poor responders (Figure 1) [29]. To date, 133 patients have finished their treatment after completion of 4 VBVP; only 20 patients received additional cycles of OPPA chemotherapy, and 6 received 40 grays radiation. The projected 3-year disease-free survival is 92% and the overall survival is 96% (Figure 2). Despite the need for a longer follow-up, these results suggest that a strategy based on primary response to treatment allows a safe decrease in therapy and that the majority of the patients can be cured with low-dose radiation therapy given after a chemotherapy devoid of mechloretamine, procarbazine and anthracyclines.

In the case of etoposide, the concern regarding the risk of secondary leukemias should not be underestimated. As far as we know to date, that risk seems dose-related and all the reported leukemias but 2 occurred after cumulative doses of more than 4 g/m². None of the studies recommend such as dose. The recent report from NCI does not give convincing arguments on the leukemogenic effects of VP16 [30]. Moreover, this drug has been given in favourable cases to replace alkylating agents whose leukemogenic risk is well established. When VP16 is given in a more advanced stage, it is given in combination with alkylating agents to improve the initial efficacy in chemotherapy in poor risk disease.

The poor prognosis Hodgkin's disease in childhood

Stage IV disease represent the first entity. As only 8% to 16% of children have stage IV, their absolute number in the published series is often small. The results of several studies demonstrated that these patient fared statistically worse than those with less advanced disease. For instance, their event-free survival was only 61% in the first French study [18] and 65% in the Toronto study [17]. The German group obtained the best results in 2 consecutive multicentric studies. They were based on surgical staging, chemotherapy with 2 cycles of OPPA and 4 cycles of COPP as previously described. Radiation therapy was given to involved nodes (25 Grays) and involved extra lymphatic organs (12 to 15 Grays).

In 1987, a SIOP study was initiated for stages IV, to reproduce, at an international level, the good German results while limiting the radiation dose to 20 Grays after a good response to chemotherapy [31]. By December 1994, 97 patients from 6 countries had been included in the study and their median follow-up was longer than 4 years. The projected 4-year survival is 95% and the disease-free survival is 79%, which is similar to the 81% observed in the previous German studies. These results confirm that OPPA-COPP chemotherapy followed by 20 Grays is a valid therapeutic approach for stages IV in children.

Refractory or relapsed disease are the second group at poor prognosis for those attempts have been made to improve the efficacy of chemotherapy by means of incorporation of new drugs in standard regimens or dose intensification with stem cell rescue. Few cytotoxic drugs appear promising in advanced Hodgkin's disease. Etoposide, already mentioned, has been included by several teams in third line therapy after MOPP and anthracycline containing regimens, such as MIME (methyl GAG, ifosfamide, methotrexate and etoposide), MINE (derived from MIME but with an increased dose of ifosfamide and VP16, vinorelbine (navelbine). These combinations, used in patients who failed after exposure to a standard chemotherapy regi-
men, yielded response rates as high as 66% and 75%, respectively.

One way to overcome relative resistance of tumour cells to cytotoxic agents is to administer very high doses of drugs with bone marrow or peripheral stem cell support. Results have been encouraging in adults with long lasting responses in refractory patients. The experience in children is limited because of the very small number of patients who enter this high-risk group. However, their outcome is not different from adults and should be treated according to the same modality [34, 35].

In conclusion, results of the recent studies suggest that the cure rate which increased considerably between 1960 and 1980 has practically reached a plateau. Since 1980, efforts have been directed toward curing the disease with a minimal amount of morbidity. The use of combined modality therapy emerged as the way to give a short, few toxic chemotherapy and low-dose limited field radiation therapy. However, it will be difficult to do much better than what is being done at present. In favourable cases, the present attempts to cure patients with chemotherapy devoid of procarbazine and adriamycin are encouraging.

For the next decade, we hope that biological advances will clarify the apparent heterogeneity of Hodgkin's disease, will offer a chance of understanding the etiology and pathogenesis of this disease, and will help continue the refinement of the therapy, thereby reducing its cost.

References


Table 1.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose/m²</th>
<th>Days</th>
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<tbody>
<tr>
<td>VP16</td>
<td>100 mg/m²</td>
<td>1, 2, 3, 4, 5</td>
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<tr>
<td>Bleomycin</td>
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<td>Vinblastin</td>
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<tr>
<td>Prednisone</td>
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<td>1 to 7</td>
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