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High Incidence of Treatment Failure With Vincristine, Etoposide, Epirubicin, and Prednisolone Chemotherapy With Successful Salvage in Childhood Hodgkin Disease

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Background and Procedure. In an attempt to further reduce the long-term toxicity of chemotherapy for childhood Hodgkin disease (HD), the Australian and New Zealand Children's Cancer Study Group between 1990 and 1996 enrolled 53 children with biopsy-proven and imaging-staged HD into a chemotherapy-only treatment regimen using 5–6 courses of vincristine, etoposide, epirubicin, and prednisolone (VEEP). ***Results.*** There were 23 events in these children with 3 progressive disease (PD), 8 partial remissions (PR), and 12 relapses. In the stage I patients, there were 8 events (35%). There was no association between the number of events and the stage of HD. Massive mediastinal disease at diagnosis was present in 16 patients, 11 of whom had an event with 3 PD, 3 PR, and 5 relapses. For all patients with an event at 6–24-month follow-up, all but two patients were salvaged with either alkylating agent-based chemotherapy alone or with irradiation and chemotherapy. The event-free survival for the whole group with median follow-up of 33 months was 59%, but only 31% for massive mediastinal disease. Disease-free survival was 78% and overall survival at 60 months was 92%, with one death due to drug-induced aplasia and another from acute myeloid leukemia. ***Conclusions.*** We conclude that VEEP chemotherapy in childhood HD used as the only treatment modality has an unacceptably high treatment failure rate in patients with massive mediastinal disease and 35% incidence of treatment failure in stage I disease. Med. Pediatr. Oncol. 32:255–258, 1999.
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INTRODUCTION

In childhood Hodgkin disease (HD), nonrandomized studies from Australia and Europe have shown that using chemotherapy-only, long-lasting, event-free survival can be achieved in approximately 70% of all stages of HD and in 60% of patients with massive mediastinal involvement [1–9]. In those who fail more intensive chemotherapy, with or without irradiation, salvage is achieved in the majority of patients [4,5,7] with overall survival ranging from 80% to 90%. Currently, the Children's Cancer Group has in progress a multicenter randomized study of chemotherapy alone vs. chemotherapy and irradiation.

There is now ample evidence of the many undesirable long-term consequences of irradiation, chemotherapy with alkylating agents, or a combination of chemotherapy and irradiation [10–13], which include dysmorphic features, cardiac disease, solid tumors, leukemia, and infertility. It is possible that with more modern methods of irradiation with reduced fields, lower doses and combination chemotherapy such as three courses of ABDV and three of MOPP, there will be lower frequency and severity of side effects [14,15], but long-term follow-up studies are not yet available.

In an attempt to reduce the long-term toxicity of chemotherapy based on alkylating agents, we have studied the effectiveness of combination therapy using vincristine, etoposide, epirubicin, and prednisolone (VEEP) without irradiation in 53 children with HD. Our hypothesis was that while the event-free survival may be reduced from 70% to 60% with this less intensive regimen, disease-free survival would remain in the range of 80%–90% because salvage with more intensive treatment is effective in HD. By using this approach, we aimed to spare the majority of patients from the most undesirable

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consequences of the more intensive chemotherapy as well as side effects of irradiation. Our results show an unacceptable rate of event-free survival in patients with bulky mediastinal disease and 35% incidence of adverse events in patients with stage I disease. We confirmed that salvage was achieved with more intensive, alkylating agent-based regimens, with or without irradiation with follow-up from time of failure of 6–18 months.

MATERIALS AND METHODS

This prospective single-regimen clinical trial commenced in September 1990 and closed in May 1996. It was proposed that, based on our previous studies in childhood HD, entry of 50 patients should permit a comparison of trends of response to treatment. The proposal was approved by the institutional ethics committees of all participating hospitals. Patients and their families gave informed consent for entry into the study. It was stated that the chemotherapy regimen was potentially less toxic than standard regimens such as MOPP or ChlVPP, and that, should there be failure to respond, salvage was likely to be successful with more intensive chemotherapy and/or irradiation. Irradiation, with or without chemotherapy, for high nodal cervical disease was given as an option for frontline treatment with a description of the possible long-term toxicity effects of irradiation and chemotherapy.

Entry into the study required biopsy confirmation of the diagnosis and staging by imaging with CT of the chest and abdomen and/or ultrasound and double-dose gallium scan. Bone marrow trephines were performed at the discretion of the principal investigators. Staging was defined by the Ann Arbor classification. Additional investigations included standard hematologic and biochemical tests and echocardiograms with the third and final course of treatment. Massive mediastinal disease was defined as a mass >1/3 the widest internal diameter on plain chest radiogram.

The chemotherapy regimen consisted of vincristine 1.5 mg/m^2 with a maximum dose of 2.0 mg on days 1 and 8; etoposide 200 mg/m^2 IV on days 1, 3, and 8 infused over 3–4 hr; epirubicin 75 mg/m^2 infused over 30 min; and prednisolone 40 mg/ m^2 from days 1–14. Cycles were repeated at 4-week intervals from the beginning of each cycle. Response to treatment was evaluated 3 weeks after completion of cycle 3 and again 6–8 weeks after cessation of therapy. Patients with early-stage disease and no mediastinal involvement received five cycles of treatment and all others received six. The evaluation after cycle 3 was restricted to radiology or imaging, while that at completion of treatment included gallium scans.

Complete remission (CR) was defined as disappearance of mass disease by clinical examination and appropriate imaging. Partial remission (PR) was defined as 75% or greater reduction of mass disease. Patients whose mass reduced by 75% or more and did not increase in size in the intervals between treatment and who continued on the same therapy were classified as PR. They were then counted as an event unless under further observation without treatment there was complete disappearance of disease; in which case they were reclassified as CR. If there was a change of treatment they were classified as PR. PD was defined as failure to respond after the third cycle of chemotherapy and included all children with less than 75% reduction in bulk disease. Relapse was classified as recurrence of disease after achieving a CR and was confirmed by imaging and by biopsy if there was clinical uncertainty. Relapse in mediastinal disease did not have to be confirmed by biopsy but was always confirmed by gallium scans.

Analysis of results was performed by Kaplan Meier method [16] with Greenwood confidence limits. Event-free survival (EFS) was defined as the time from diagnosis to PD, PR requiring change of treatment, relapse, or death. Disease-free survival (DFS) was defined as time from achieving CR to relapse or death. Overall survival (OS) was defined as time from diagnosis to death.

TABLE I. Events According to Stage of Disease

Stage	Number of events/total	Progressive disease	Partial remission	Relapse
I	8/23 (35%)	0	1	7
II	4/14 (29%)	0	2	2
III	3/5 (60%)	2	1	0
IV	8/11 (73%)	1	4	3
Total	23/53 (43%)	3	8	12

RESULTS

Fifty-five patients were registered but two (4%) elected not to participate in the study, one choosing irradiation only and the other MOPP chemotherapy without irradiation. Of the 53 evaluable patients, there were 39 (74%) males and 14 (26%) females. The median age at diagnosis was 12 years with a range of 3.5–16. Massive mediastinal disease was present in 16 (30%). The clinical staging is shown in Table I. Histologic examination of biopsy specimens showed nodular sclerosing disease in 31 (58%), mixed cellularity in 16 (30%), lymphocyte depletion in 1 (2%), and lymphocyte predominance in 5 (9%).

There have been 23 (43%) events in the 53 patients with PD in 3 (6%), PR in 8 (15%), and relapse in 12 (23%). Events according to stage are shown in Table I. In patients with stage I and II disease, relapses were the most common, while in those with stage III and IV, PR and PD predominated. There was no relationship evident between histological subtype and outcome and only 10

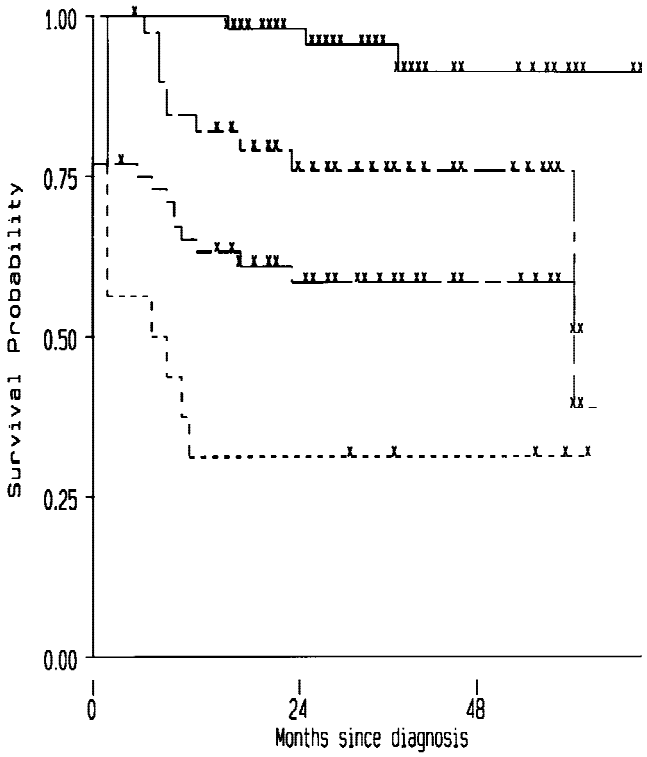

Fig. 1. Overall survival (top line); disease-free survival (second line); event-free survival (third line); and event-free survival for massive mediastinal disease (bottom line).

(19%) of patients presented with B-symptoms with no apparent relationship to response. Of the 12 patients in PR at completion of three cycles of chemotherapy, 8 were still in PR after six cycles and had their therapy changed and 4 achieved CR and remain event free at 12–58 months from diagnosis.

Bulky mediastinal disease was associated with a higher failure rate but not bulky disease at other sites. The EFS, DFS, and OS for all patients are shown in Figure 1. The EFS was 59% (confidence limits [CI], 0.44–0.71) at median follow-up of 33 months with two late events beyond 60 months. The DFS was 78% (CI, 0.59–0.87) at median follow-up of 28 months. The OS was 92% (CI, 0.75–0.97) at 60 months

The hematologic toxicity of the regimen was moderate and adequately documented in 38 patients. Neutropenia < 0.5×10^9/L occurred in 12 (32%) of 38 patients with 8 admissions for antibiotic therapy, but no episodes of septicemia. Anemia requiring transfusion occurred in four (11%). There were no episodes of thrombocytopenia and no reports of abnormal echocardiograms. Alopecia and mild emesis were common.

The response to treatment in patients with massive mediastinal disease showed a substantial difference compared to those without mediastinal widening or widening less than 1/3 of the internal thoracic diameter. In the 16 patients with massive mediastinal disease, there have been 11 (69%) events with PD in 3 (19%), PR in 3 (19%) and relapse in 5 (32%). The EFS with massive mediastinal disease, shown in Figure 1, was 31%. The results of salvage therapy with follow-up from the event of 6–24 months were as follows: one with PD was treated with MOPP and died of chemotherapy toxicity while in remission; another achieved CR with six courses of MOPP/ABVD but 2 years after change of treatment died from acute myeloid leukemia (AML) with cytogenetics of the leukemic cells showing t9;11(p21;q23). The third achieved stable CR with total nodal irradiation and autologous transplant. Of the three with PR and five with relapse, five achieved CR with a variety of alkylating agent chemotherapy regimens, two with mantle irradiation and chemotherapy, and one with marrow ablative chemotherapy and peripheral blood stem cell rescue.

In the 12 patients without massive mediastinal disease who suffered events, there were no instances of PD. Of the five with PR and seven with relapse, all achieved CR with a change of therapy, eight with alkylating agent chemotherapy, two with irradiation and chemotherapy, and two with irradiation only.

DISCUSSION

The response to VEEP chemotherapy for bulky mediastinal disease and the high incidence of relapse in stage I disease (7/23, Table I) is disappointing and confirms the data presented by British investigators [5,15] for adult and pediatric HD. In previously untreated pediatric patients, 62% achieved CR; of the four patients who had a delayed CR, three relapsed. Two other children who achieved early CR also relapsed, with a relapse-free rate at 3 years of 67%. In adults the confirmed and unconfirmed complete response rate with median follow-up of 45 months was 71% and failure-free survival was 62%, with patients in confirmed CR having a higher failure-free survival at 5 years (88%) vs. those in unconfirmed failure-free survival of 56%. Unlike our study, the etoposide in the British studies was given mainly orally and as a consequence it may have been considered that the variable bioavailability of the oral preparation may have diminished the effectiveness of the chemotherapy regimen. Our results with IV etoposide suggest, however, that the VEEP regimen is less effective in HD than the alkylating agent-based regimens. Furthermore, death from AML in one of our patients who received alkylating agent therapy as well as etoposide raises the possibility that the combination of etoposide and alkylating agents increases the probability of inducing early-onset posttherapy leukemia.

The EFS of 31% in patients with massive mediastinal disease was markedly inferior to the 60% reported by us for MOPP or EVAP/ABV [3,4,7] and the 17% relapse rate reported with MOPP or MOPP/ABVD chemo-

therapy followed by 20 Gy involved field irradiation [15]. The results from the Stanford group, using three cycles of ABVD and three of MOPP and irradiation to 25 Gy to bulky sites after two cycles of chemotherapy, while not reporting results in massive mediastinal disease, report a 69% EFS in stage IV disease and 93% in stage I–III disease [14].

Death from the toxic effects of salvage occurred in one patient with PD and another with PR who subsequently was treated with alkylating agents and developed AML with t(9;11), a translocation previously reported to be associated with alkylating agent chemotherapy for Hodgkin disease [17]. In a previous study reported by us on EVAP/ABV [4], there were no toxic deaths and no secondary leukemias. Despite the small numbers of patients, it is likely that etoposide-based regimens without alkylating agents may not only be less effective but also increase the risk of secondary leukemia when salvage is required with alkylating agent-based chemotherapy.

Of the 23 patients who experienced a disease-related event, 21 were salvaged with OS of 92%. It could be argued that the VEEP regimen prevented exposure to the most toxic therapy modalities in 30 patients and that this justifies an approach in which approximately 40% of patients will require either double exposure to chemotherapy or additional irradiation. The high proportion of therapy failures with the VEEP protocol does not undermine the search for the less toxic therapy approaches to HD, but rather emphasizes the need to balance the risks and benefits of non–alkylating agent-based chemotherapy regimens and to test combinations of agents with established activity or similar cytotoxic mechanisms with the least long-term toxicities. As a result of our experience with VEEP, we are piloting a study based on a previous pilot protocol known as EVAP/ABV [4] using vincristine, doxorubicin, etoposide, cytarabine, cisplatin, and prednisolone for patients with stage I and II disease and a hybrid MOPP/ABV regimen for patients with stages III and IV and with massive mediastinal disease.

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REFERENCES

1. Olweny CLM, Katongole-Mbidde E, Kiine C, et al. Childhood Hodgkin's disease in Uganda: a ten year experience. Cancer 1978; 42:787–792.
2. Ekert H, Waters KD. Results of treatment of 18 children with Hodgkin's disease with MOPP chemotherapy as the only treatment modality. Med Pediatr Oncol 1983;11:322–326.
3. Ekert H, Waters KD, Smith PJ, et al. Treatment with MOPP or ChlVPP chemotherapy only for all stages of Hodgkin's disease. J Clin Oncol 1988;6:1845–1850.
4. Ekert H, Fock T, Dalla-Pozza L, et al. A pilot study of EVAP/ABV chemotherapy in 25 newly diagnosed children with Hodgkin's disease. Br J Cancer 1993;67:159–162.
5. O'Brien LR, Pinkerton CR, Kingston J, et al. VEEP in children with Hodgkin's disease: a regimen to decrease late sequelae. Br J Cancer 1992;65:756–760.
6. Behrendt H, Brinkhius M, Van Leeuwen EF. Treatment of childhood Hodgkin's disease with ABVD without radiotherapy. Med Pediatr Oncol 1996;26:244–248.
7. Ekert H. Massive mediastinal Hodgkin's disease in childhood: results from four Australian oncology centers, 1972–1993. Cancer Res Therapy Control 1996;5:41–47.
8. Pavlovsky S, Maschio M, Santarelli MT, et al. Randomised trial of chemotherapy versus chemotherapy plus radiotherapy for stage I–II Hodgkin's disease. J Natl Cancer Inst 1988;80:1466–1472.
9. Van den Berg H, Stuve W, Behrendl H. Treatment of Hodgkin's disease in children with alternating mechlorethamine, vincristine, procarbazine and prednisone (MOPP) and adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) courses without radiotherapy. Med Pediatr Oncol 1997;29:23–27.
10. Hancock SL, Donaldson SS, Hope RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 1993;11:1208–1215.
11. Bhatia S, Robinson LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996;334:745–753.
12. Meadow AT, Obringer AC, Marrero O, et al. Second malignant neoplasms following Hodgkin's disease: treatment and splenectomy as risk factors. Med Pediatr Oncol 1989;17:477–484.
13. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 1996;27:74–78.
14. Hunger SP, Link MP, Donaldson SS. ABVD/MOPP and low dose involved field radiotherapy in paediatric Hodgkin's disease: the Stanford experience. J Clin Oncol 1994;12:2160–2166.
15. Oberlin O, Leverger G, Pacqurement H, et al. Low dose radiation therapy and reduced chemotherapy in childhood Hodgkin's disease: the experience of the French Society of Pediatric Oncology. J Clin Oncol 1992;10:1602–1608.
16. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;54:457–481.
17. Pui C-H, Hancok ML, Raimondi SC, et al. Myeloid neoplasia in children treated for solid tumors. Lancet 1990;336:417–421.