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Eur J Cancer, Vol. 28A, No. 10, pp. 1727–1729, 1992.
Printed in Great Britain

ABEP as Primary Chemotherapy for Hodgkin's Disease

Gilbert B. Zulian, Bernadette Mermillod and Pierre Alberto

20 untreated Hodgkin's disease patients and 1 patient relapsing after radiotherapy (17 stage IIB–IV and 4 stage I–IIA) were given doxorubucin, bleomycin, etoposide and prednisone on a 21-day cycle. The response rate was 95% and 16 patients (76%) achieved complete remission. 4 patients have relapsed 2, 5, 22 and 50 months after treatment. Survival was 100% at a median follow-up of 35 months. However, due to dyspnoea on exertion in 2 patients, bleomycin will be abandoned, and the occurrence of two second malignancies questions the role of etoposide as a leukaemogenic agent.

Eur J Cancer, Vol. 28A, No. 10, pp. 1727–1729, 1992.

INTRODUCTION

DRAMATIC IMPROVEMENT in the management of Hodgkin's disease (HD) has been made over the past 20 years with the use of mechloretamine, vincristine, procarbazine and prednisone (MOPP) and similar chemotherapy regimens [1, 2]. However, long term results show an increase in the occurrence of second malignancies [3]. Such toxicity has so far not been the case with ABVD and this regimen has become a valid alternative to MOPP [4]. Furthermore, ABVD is apparently non-cross-resistant to MOPP despite the close relationship between vincristine and vinblastine, and procarbazine and dacarbazine.

The latest chemotherapeutical advance in the past few years comes with the use of etoposide which has emerged as a very active drug for HD, either as single agent [5] or in combination with other agents [6–8].

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Revised and accepted 18 Feb. 1992.

In order to develop a new combination containing active drugs with different mechanism of cytotoxicity, we have built the ABEP regimen with doxorubicin, bleomycin, etoposide and prednisone.

PATIENTS AND METHODS

From January 1984 until December 1990, 21 patients requiring chemotherapy for Hodgkin's disease were treated at our institution. 20 patients were previously untreated and 1 was relapsing from radiotherapy. 12 patients were males and the median age was 37 years (range 18–64 years). Investigations included clinical examination, full blood count and erythrocyte sedimentation rate, biochemistry and liver function tests, chest X-ray and computed tomography (CT) scan, abdominal ultrasound or CT scan, bone marrow trephine and aspirate, and appropriate biopsy for histological diagnosis.

15 patients had nodular sclerosis, 3 had mixed cellularity, 2 had lymphocytic predominance and one remained undefined. The majority of patients had advanced disease, 3 with stage IVB, 4 with stage IIIB, 6 with stage IIIA, 4 with stage IIB, 3 with stage IIA and 1 with stage IA.

Doxorubucin was given at a mean dose of 48 mg/m^2 (range 30–65 mg/m^2) intravenously on day 1. Bleomycin was given at a mean dose of 8 mg/m^2 (range 5–18 mg/m^2) intravenously on days 1, 2 and 3 for 10 patients and days 1, 8 and 15 for 11 patients. Etoposide was given at a mean dose of 105 mg/m^2 (range 90–140 mg/m^2) intravenously over 1 h on days 1, 2 and 3. Antiemesis with dexamethasone and metochlopramide was routinely provided. Patients also received oral prednisone 100 mg total dose on days 1–5. A median of six courses (range 2–8 courses) was given on a 21-day cycle basis for a total of 113 courses. The total cumulative dose of bleomycin a patient could receive was limited to 200 mg.

RESULTS

Response and survival (Fig. 1)

Overall response rate to ABEP was 95% with 16 complete responses (76% CR), 4 partial responses (19% PR) and one with no response (5% NR).

9 CR patients with bulky disease at presentation received adjuvant radiotherapy as a consolidation measure.

4 patients among the 16 CRs (25%) relapsed at 2, 5, 22 and 50 months after completion of doxorubicin, bleomycin, etoposide and prednisone (ABEP). These patients had mediastinal involvement at presentation. They were offered second-line chemotherapy.

PR and NR patients received second-line chemotherapy and/or radiotherapy. 4 out of 5 patients achieved CR and the last one further PR. None has relapsed nor progressed so far.

Survival for the entire group is 100% at a median follow-up of 35 months (range 11–84).

Toxicity

In most cases, nausea and vomiting were successfully prevented. Alopecia was universal. Leukopenia grade 4 was recorded in 1 case, grade 3 in 6 cases and grade 2 in 13 cases. Thrombocytopenia grade 1 occurred only once. Mucositis grade 3 occurred in 1 case and grade 2 in 2 cases. 2 patients had dyspnoea on exertion.

Second malignancies (Table 1)

1 patient in PR after ABEP had to receive second line MOPP chemotherapy and radiotherapy to achieve CR. 32 months later, acute non-lymphoblastic leukemia was diagnosed. No chromosomal abnormality was detected on karyotype. To date, this patient is still alive.

1 patient in CR after ABEP had an early relapse. This was successfully treated with salvage MOPP chemotherapy and second CR was achieved. 17 months later, myelodysplastic syndrome with chromosomal abnormalities [t (6;9) (p23;q34)] was diagnosed and the patient was considered eligible for HLA matched sibling allogeneic bone marrow transplantation.

In contrast, none among 8 patients in CR after ABEP only and no adjuvant therapy has so far developed a second malignancy.

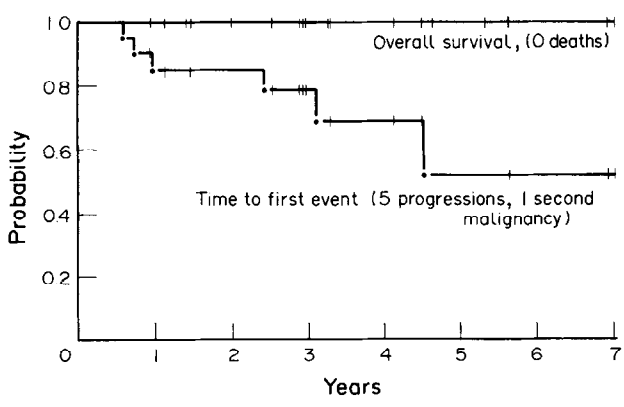

Fig. 1. Survival of 21 patients with Hodgkin's disease after ABEP.

Table 1. Second haematological malignancies

Sex, age, histology, stage	Treatment	2nd malignancy
Female, 48 years, IIIA, lymphocytic predominance	ABEP × 3 = PR MOPP × 2 = CR Mantle irradiation	ANLL (normal karyotype)
Female, 28 years, IIB, nodular sclerosis	ABEP × 7 = CR MOPP × 4 = CR	MDS (t(6;9) (p23;q34)

ABEP = Doxorubicin, bleomycin, etoposide and prednisone.
MOPP = Mechloretamine, vincristine, procarbazine and prednisone.
ANLL = Acute non-lymphoblastic leukaemia.
MDS = Myelodysplastic syndrome.
PR = Partial response.
CR = Complete response.

DISCUSSION

ABEP chemotherapy regimen was selected through the high single agent activity of each drug in HD. The apparent different mechanism of action and acquisition of cell resistance made it an attractive combination.

Accordingly, ABEP was very active both in terms of response rate and overall survival. However, neither relapse nor primary resistance could be overcome in some cases. Mediastinal involvement at presentation was a feature of every relapsing patients, despite adjuvant radiotherapy in 2 cases. Primary resistance, partial or complete, to ABEP occurred in patients characterised by infradiaphragmatic involvement. This led to the use of second line alkylating agent-based chemotherapy, i.e. MOPP. As a major drawback of such a strategy, 2 out of 7 patients who received both ABEP and MOPP developed a second haematological malignancy as a probable direct consequence. Nowadays, such a high proportion of early malignancy appears unacceptable in an otherwise curable disease. Although allogeneic bone marrow transplantation is available in these cases [9, 10], this represents yet another added toxicity.

Leukemogenicity of etoposide has been recently suspected after chemotherapy for solid tumours [11, 12] and also lymphoblastic leukaemia [13]. Some of these myeloid leukaemias had characteristic chromosomal abnormalities different from the one detected by us. To our knowledge, such a complication has not been reported in HD treated with first-line etoposide in combination [14].

Further studies are required prior to assuming etoposide to be leukaemogenic *per se* and to better define the possible additional leukaemogenic effect of etoposide and alkylating agents.

Our study, albeit small, suggests ABEP to be sufficiently active in order to be used in chemotherapy naive patients with HD. Second malignancies have so far only been seen in patients receiving MOPP as salvage treatment. None of our patients has died neither from HD nor from complications to date and the projected survival should be similar to the published literature.

In our opinion, an etoposide-based combination without alkylating agents should be used as first-line chemotherapy in

HD. In case a second-line chemotherapy is required, MOPP is probably not the best combination, since second haematological malignancies can develop.

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Acknowledgements—The authors gratefully thank Ms Melissa Morawitz for expert secretarial assistance, and Dr Reto Abelé for his help in preparing the data.

Eur J Cancer, Vol. 28A, No. 10, pp. 1729–1734, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Changes of Lymphocyte Subsets after Local Irradiation for Early Stage Breast Cancer and Seminoma Testis: Long-term Increase of Activated (HLA-DR+) T Cells and Decrease of "Naive" (CD4-CD45R) T Lymphocytes

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Blood lymphocyte subsets of early breast cancer patients and of men with stage I seminoma of the testis were studied up to 6 years after radiotherapy. Similar results were obtained in the two patient groups. After a temporary decrease, the CD4-w29 or "memory" T cells recovered completely, while the CD4-45R or "naive" T cells remained decreased up to 6 years after irradiation. The number of CD8 T lymphocytes did not change during or after treatment. Because of the decrease of a subset of CD4 cells, and the unchanged values of CD8 cells, the CD4/CD8 ratio decreased significantly after irradiation, and remained lower than before treatment up to 5–6 years after radiotherapy. The number of both HLA-DR positive CD4 and HLA-DR positive CD8 T cells ("activated" T cells) increased significantly after irradiation. The natural killer (NK) cells were not affected by treatment. We propose that the recovery of the CD4 cells is limited to the CD4-w29 ("memory") population because of thymic dysfunction in older humans. The impact of the observed immune modulation on the low susceptibility for infections after local irradiation, and on putative antitumour immune responses is discussed.
Eur J Cancer, Vol. 28A, No. 10, pp. 1729–1734, 1992.

INTRODUCTION

SEVERAL INVESTIGATORS have described changes in the lymphocyte populations after local radiotherapy in humans [1–4]. A lymphopenia and a decreased CD4/CD8 ratio were the most striking observations. To investigate in more detail the changes of lymphocyte subgroups after clinical radiotherapy, we initiated a study in irradiated stage I–II breast cancer and stage I seminoma testis patients. Patients with seminoma testis were included in the study to investigate the possible influence of sex (male), age (generally a young population), and location (thoracic vs. infradiaphragmatic fields) on the immune changes after radiotherapy. We not only wanted to verify the previously