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Salvage chemotherapy of refractory non-Hodgkin's lymphoma with aclacinomycin, behenoyl ara-C, etoposide, and prednisolone

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Summary. A total of 40 patients with recurrent non-Hodgkin's lymphoma were treated with ABEP combination chemotherapy (aclarubicin, N^4-behenoyl-1-β-D-arabinofuranosylcytosine, etoposide, and prednisolone). A complete remission (CR) was achieved in 37.5% of the patients and partial remission, in 15.0%. The ABEP regimen proved to be effective in T-cell as well as B-cell lymphoma. It appears that the ABEP regimen may be partially non-cross-resistant with front-line doxorubicin-containing combinations. Survival for 39 months was achieved in 42.0% of the CR responders compared with 6.7% of partial responders (PRs) and nonresponders (NRs) ($P < 0.01$). Diesease-free survival for 45 months was seen in 66% of the CR patients. The ABEP regimen was effective in the treatment of patients with recurrent or refractory lymphoma, enabling hope for long-term survival in the majority of CR cases.

Introduction

Substantial improvements have been achieved in the management of patients who present with advanced-stage non-Hodgkin's lymphoma (NHL). Aggressive combination chemotherapy protocols such as M-BACOD [21] (methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), MACOP-B [14] (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), and ProMACE-MOPP [5] (mechlorethamine, doxorubicin, cyclophosphamide, etoposide, methotrexate, vincristine, procarbazine, and prednisone) have dramatically improved the percentage of NHL patients responding with complete remissions (CR). However, randomized trials have not revealed significant increases in such patients relative to those treated with less intensive survival regimens such as CHOP [11] (cyclophosphamide, doxorubicin, vincristine, and prednisone).

In spite of these improved results, the prognosis in patients with advanced lymphoma (especially in the leukemic state) is failure of response or relapse after these regimens. Therefore, effective salvage protocols are still in great demand; most of these mainly use drugs that patients have received in prior therapy.

We designed this study to assess the efficacy of a four-drug combination regimen including aclarubicin, N^4-behenoyl-1-β-D-arabinofuranosyl-cytosine (BHAC), etoposide, and prednisolone as an intensive salvage regimen (ABEP) for the treatment of patients with relapsed or refractory NHL. Aclarubicin is a relatively new anthracycline antibiotic active against NHL [17]. Similarly, etoposide is active against NHL [10] when used singly. BHAC is a lipophilic, deaminase-resistant derivative of 1-β-D-arabinofuranosylcytosine (ara-C). Although the exact antitumor mechanism of BHAC has not been completely elucidated, this agent appears to be activated when metabolized to form ara-C [6], but it may also be activated through its direct phosphorylation to form BHAC-triphosphate [15]. Ara-C is also active against NHL [1] when used singly. Thus, each of these drugs is active when used singly in the treatment of patients with advanced NHL; in combination, they are free of overlapping patterns of toxicity because of their different underlying toxic mechanisms.

Materials and methods

A total of 40 patients with advanced aggressive NHL who failed to respond to or relapsed after first-line chemotherapy given between April 1984 and July 1988 were evaluated in this study. The major patient characteristics are listed in Table 1. In all, 22 cases of diffuse large-cell disease were included in the intermediate-grade group. All patients had previously received CHOP [11] or CHOP-Bleo (Adriamycin: 300–450 mg/m^2 in relapsed cases).

Before initiation of the treatment, patients were screened according to the following criteria: (1) existence of a measurable lesion as an indicator of drug response; (2) a lapse of more than 4 weeks after completion of the preceding chemotherapy and/or radiotherapy; (3) a Karnofsky performance status of ≥30%; and (4) adequate renal, hepatic, and cardiac function except when the kidney, liver, or heart showed tumor involvement.

The treatment was carried out on a dose regimen, on which aclacinomycin was given i.v. at a dose of 15 mg/m^2 on days 1–7; BHAC, at a dose of 200 mg/m^2 by a 6-h infusion on days 1–7; etoposide, at 70 mg/m^2 i.v. on days 1–5; and PSL, at 20 mg/m^2 p.o. on days 1–7. All patients

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Table 1. Patient characteristics (a working formulation of non-Hodgkin's lymphoma)

Characteristic	Number of patients (%)
Evaluated	40
Age, median (range)	56 years (19–78)
Sex:	
M	30 (75.0)
F	10 (25.0)
Clinical stage:	
III	15 (37.5)
IV	25 (62.5)
Histology:	
Low-grade	5 (12.5)
Intermediate-grade	29 (72.5)
High-grade	6 (15.0)
Surface marker:	
T-cell	10 (25.0)
B-cell	17 (42.5)
Unclassified	3 (7.5)
Not done	10 (25.0)
Response to prior chemotherapy:	
Relapsed	17 (42.5)
Refractory	23 (57.5)

were hospitalized for this therapy. If severe myelosuppression (>300 granulocytes/μl over 5 days) had developed during the preceding cycle, the doses of aclacinomycin and BHAC were decreased by 20% for each subsequent cycle. ABEP was given for up to three cycles or until disease progression was observed. Patients who responded to ABEP with complete remissions (CRs) or partial response (PRs) subsequently received consolidation chemotherapy over seven cycles or until cardiac toxicity or disease progression occurred.

The patients were evaluated before each course by physical examination, roentgenography, computerized tomographic scans, and hematological and biochemical studies. A CR was defined as the disappearance of all clinical evidence of tumor for at least 1 month. The duration of survival and that of remission were calculated from the beginning of ABEP therapy. Patients who died early in the course of the treatment were considered to be treatment failures for the purpose of survival calculation, which was carried out according to the method of Kaplan and Meier [12]. The survival for distinct patient groups were compared using the generalized Wilcoxon test [7].

Results

The response to treatment was evaluable in 40 patients. Major responses were achieved in 21 (52.5%) of the patients (15 CRs, 37.5%; 6 PRs, 15.0%). The responses by sex, clinical stage (Ann Arbor classification), histology (working formulation of non-Hodgkin's lymphoma), surface marker, and response to prior chemotherapy are listed in Table 2. A CR was documented in 9 (60.0%) of 15 patients with lesions confined to clinical stage III and in 6 (24.0%) of 25 with clinical stage IV lesions ($P < 0.05$). CRs were then documented in 11 (74.7%) of 17 patients who relapsed after prior chemotherapy and in 4 (17.4%) of 23 cases of refractory disease ($P < 0.05$). It is remarkable that the response rate in T-cell lymphoma was the same as that in B-cell lymphoma. As depicted in Fig. 1, the median survival of all patients was 4 months. A 39-month survival was achieved in 42.0% of patients who achieved a CR com-

Table 2. Response to ABEP in 40 evaluable patients with refractory non-Hodgkin's lymphoma

	Patients (*n*)	CR (%)	PR (%)	NR (%)	RR (%)
Total	40	15 (37.5)	6 (15.0)	19 (47.5)	21 (52.5)
Sex:					
M	30	11 (36.7)	5 (16.7)	14 (46.7)	26 (86.7)
F	11	4 (36.4)	2 (18.2)	5 (45.5)	6 (54.5)
Clinical stage:					
III	15	9 (60.0)	2 (13.3)	3 (20.0)	11 (73.3)
IV	25	6 (24.0)*	5 (20.0)	15 (60.0)	11 (44.0)
Histology:					
Low-grade	5	1 (20.0)	0	4 (80.0)	1 (20.0)
Intermediate-grade	29	12 (41.4)	6 (20.7)	11 (37.9)	18 (62.1)
High-grade	6	2 (33.3)	0	4 (66.7)	2 (33.3)
Surface marker:					
T-cell	10	2 (20.0)	2 (20.0)	6 (60.0)	4 (40.0)
B-cell	17	6 (35.3)	3 (17.6)	8 (47.1)	9 (52.9)
Response to prior chemotherapy:					
Relapsed	17	11 (74.7)	1 (5.9)	4 (23.5)	12 (70.6)
Refractory	23	4 (17.4)*	5 (21.7)	15 (65.2)	49 (39.1)

CR, complete remission; PR, partial response; NR, no response; RR, response rate
* $P < 0.05$

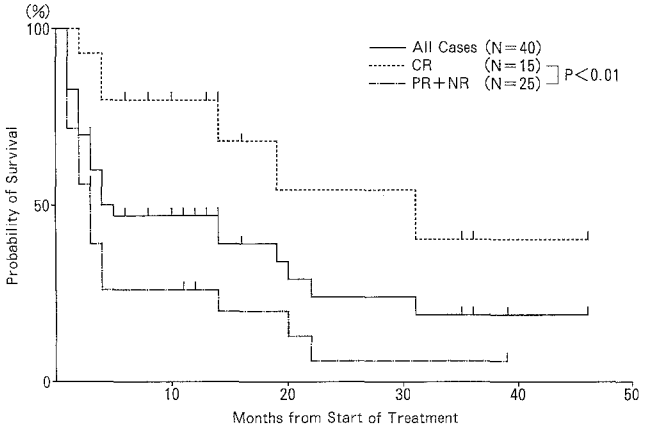

Fig. 1. The survival of the 15 patients who achieved a CR following ABEP was significantly longer ($P < 0.01$) than that of the 25 patients who failed to do so

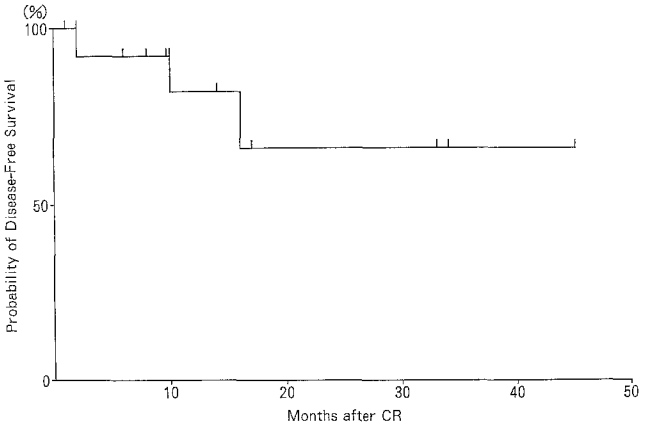

Fig. 2. Disease-free survival of complet responders treated with ABEP

pared with 6.7% of PRs and nonresponders (NRs). The comparison of survivals in patients who achieved CRs vs PRS + NRs revealed a statistically significant difference ($P < 0.01$). A 20-month survival was achieved in 43.8% of the patients who suffered a relapse, compared with 17.3% of refractory patients ($P < 0.05$). However, the differences in clinical stage, histology and surface marker were not statistically significant. As depicted in Fig. 2, disease-free survival for 45 months was seen in 66% of the 15 patients attaining CR, with relapses occurring only in 3.

Table 3 presents the adverse reactions to ABEP therapy. In general, this therapy was well tolerated, and none of the patients refused treatment. The major toxicity was myelosuppression, which was severe due to bone marrow involvement by lymphoma cells. Severe neutropenia occurred in 28 patients (70%), resulting in bacterial or fungal infection in 12, who then received antibiotic therapy; of patients with documented infection, 6 died of septic complications. Transient elevations of liver enzymes (SGOT, SGPT, and alkaline phosphatase) were documented in four patients (10%) , but all were spontaneously reversible. Tachycardia and arrhythmia were also observed in three patients.

Table 3. Toxicities of ABEP therapy

Manifestation	Number of patients (%)
Hematologic:	
Neutropenia (nadir, <300 granulocytes/μl)	28 (70.0)
Thrombocytopenia (nadir, <20,000 platelets/μl)	18 (45.0)
Hair loss	32 (80.0)
Nausea	27 (67.5)
Stomatitis	17 (42.5)
Anorexia (severe)	12 (30.0)
Hepatotoxicity	4 (10.0)
Cardiac toxicity	3 (7.5)

Discussion

The results of this study showed that the ABEP regimen (aclarubicin, BHAC, etoposide, and prednisolone) is effective in the treatment of patients with relapsed or progressive NHL. Issell and Crooke [10] used etoposide alone in their previous treatment of patients with NHL, reporting a response rate of 31% in 85 patients with histiocytic lymphoma and that of 10% in 31 patients with lymphocytic and mixed lymphoma. Schmoll et al. [20] reported an overall response rate of 29% in 216 patients with previously treated NHL.

Aclarubicin is an anthracycline antibiotic, isolated from *Streptomyces galilaeus*, which has proved to be less cardiotoxic than doxorubicin or daunorubicin in animal experiments [11] and differs from other anthracycline antibiotics in its chemical structure and biological activities [18]. The drug accumulates predominantly in the cytoplasm and inhibits RNA synthesis in vitro at a much lower concentration than that required for inhibition of DNA synthesis [18]. It interferes with the late S/G_2 and G_1 phase of the cell cycle [23]. Furthermore, this drug has been shown to be non-cross-resistant with other anthracyclines in clinical studies [19]. It is known that multidrug combination chemotherapy including ara-C (e.g., COMLA [22], A-COMLA [16]) produces a good response rate in NHL.

BHAC is an analogue of ara-C and is cell-cycle-specific. The pharmacokinetic study of BHAC in humans has revealed a prolonged plasma half-life and a slow plasma clearance [24]. In contrast, ara-C has been reported to clear rapidly from plasma [8]; thus, continuous infusion of BHAC is not necessary. In addition, the adverse reactions to BHAC seem much milder than those to ara-C [13]. CR has been difficult to achieve with salvage therapy in resistant NHL. However, the ABEP regimen documented a high CR rate, especially in clinical stage III (60.0%) and relapsed cases (74.7%). Furthermore, CRs and PRs were achieved in a large number of patients with T-cell lymphoma, where CRs are harder to obtain [9] than in B-cell lymphomas. The duration of the CRs achieved with ABEP was satisfactory. The results suggest the lack of cross-resistance with the front-line regimen used, including Adriamycin-based combinations in all cases. This indicates that ABEP is at least partially non-cross-resistant with doxorubicin-containing combination regimens.

The disease-free survival of patients who achieved a CR, as well as that for the whole group, was not inferior to our previous experience with etoposide-containing combinations [2, 25]. When some groups were divided by three histologic or two surface markers, the overall and disease-free survival achieved were not statistically significant because many cases of large-cell disease were included in the intermediate-grade group. Our results show that the prognostic characteristics of patients treated with the ABEP regimen were less favorable. The disease-free survival of patients responding with CRs was very favorable, indicating that the ABEP regimen may be curative in the majority of CR cases. The ABEP regimen was associated with substantial toxicity. This was not surprising to our patients, and in no case was chemotherapy discontinued due to toxicity.

In summary, the ABEP regimen produced a 52.5% overall response rate and a CR rate of 37.5%. This regimen is probably partially non-cross-resistant with front-line doxorubicin-containing combinations. It is effective in the management of relapsed patients, enabling hope for long-term survival in the majority of CR cases. Because a high CR rate and a long disease-free survival were achieved in relapsed cases, further ABEP regimens may be optimized by their use as first-line protocols or as one arm of a protocol of alternating regimens.

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