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m-BACOD chemotherapy for intermediate- and high-grade non-Hodgkin's lymphoma

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Summary. A total of 92 patients with previously untreated intermediate- or high-grade non-Hodgkin's lymphoma attending the University Department of Medicine, Queen Mary Hospital, Hong Kong, were treated with the m-BACOD chemotherapy regimen (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone). Additional involved-field radiotherapy was given to 32 (35%) patients. Myelosuppression was the major toxicity, and 5 (5%) treatment-related deaths occurred due to pneumonia, bleomycin sensitivity, doxorubicin cardiotoxicity and reactivation of hepatitis B infection. The overall complete response (CR) rate was 65/92 (71%) and the relapse rate was 22/65 (34%). The disease-free survival of the 65 CR patients at 2 years was 52% and the overall survival of all 92 patients at 3 years was 56%. The CR rate of stage I and II patients was significantly better than that of those with stage III and IV disease (87% vs 59%; $P=0.01$), and the CR rate of stage III patients was superior to that of those with stage IV disease (86% vs 50%; $P=0.05$). The overall survival of stage III and IV patients was significantly worse than that of subjects with stage I and II disease (31% vs 73%; $P=0.02$). Multivariate analysis revealed that the independent prognostic variables significantly determining the CR rate and survival included the clinical stage and the serum lactate dehydrogenase level. From this study, the results of treatment with the m-BACOD regimen in patients with advance disease appeared to be similar to those obtained using the conventional CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone).

Introduction

The first generation of combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine and prednisone) have been successful in achieving long-term remission and probable cure in roughly one-third of patients with aggressive non-Hodgkin's lymphoma (NHL) [1, 11, 13]. Attempts have been made to improve the treatment results by using newer chemotherapy regimens that consist of six or more active drugs, and the early results are impressive [1, 2, 10, 14]. This paper reports the results we obtained using one of these regimens, m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), in 92 evaluable patients with intermediate- and high-grade NHL.

Patients and methods

From January 1986 to June 1990, 92 patients with previously untreated intermediate- or high-grade NHL attending the University Department of Medicine, Queen Mary Hospital, Hong Kong, were treated with the m-BACOD chemotherapy regimen. All subjects were <65 years of age and showed satisfactory cardio-pulmonary, renal and hepatic function and a performance score of ≤ 2 (WHO scale) before the start of treatment [6]. The pathological materials were classified according to the Working Formulation (WF) [12]. Whenever fresh and unfixed specimens were available, the immunophenotype was determined by the immunoperoxidase technique using a panel of commercially available monoclonal antibodies [5].

Patients were staged according to the Ann Arbor system [3]. Clinical staging procedures included a history and physical examination, full blood counts, blood biochemistry, a bilateral iliac-crest trephine biopsy and a bone marrow aspirate. Computerised axial tomography was performed to detect abdominal lesions. Barium studies and/or endoscopic examinations were done when gastrointestinal involvement was suspected. Laparotomy was not routinely performed.

Patients received the m-BACOD chemotherapy, consisting of 4 mg/m^2 bleomycin given i.v. on day 1, 45 mg/m^2 doxorubicin given i.v. on day 1, 600 mg/m^2 cyclophosphamide given i.v. on day 1, 1 mg/m^2 vincristine given i.v. on day 1, 6 mg/m^2 dexamethasone given orally on days 1–5, 200 mg/m^2 methotrexate given i.v. on days 8 and 15, and 10 mg/m^2 folinic acid given orally every 6 h for six doses starting exactly 24 h after methotrexate administration. The treatment was repeated every 21 days [2, 14]. Patients with initially localised (stage I and II) or bulky disease were given additional involved-field radiotherapy following chemotherapy.

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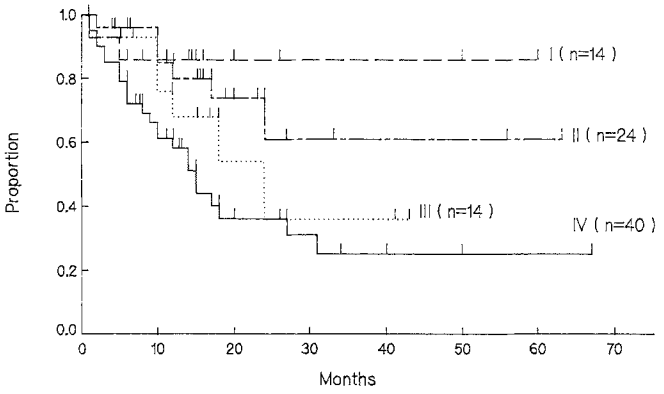

Fig. 1. The overall survival curves for 92 patients receiving the m-BACOD regimen, platted according to clinical stage

Table 1. The results of m-BACOD chemotherapy in patients with intermediate- and high-grade non-Hodgkin's lymphoma according to clinical stage

	Stage I	Stage II	Stage III	Stage IV
CR rate	14/14 (100%)	19/24 (79%)	12/14 (86%)	20/40 (50%)
Relapse rate:	5/14 (36%)	6/19 (32%)	4/12 (33%)	7/20 (35%)
DFS of CR patients at 2 years	55%	58%	59%	40%
Overall survival of patients at 3 years	86%	61%	36%	25%

Tumour response was assessed using standard criteria [6]. The Kaplan-Meier product-limit method [7] was used to generate disease-free survival (DFS) and overall survival curves. DFS was measured from the date of first remission to the date of first relapse. The overall survival was measured from the date of diagnosis to the date of death or last follow-up. The log-rank procedure was used to compare survival curves and the chi-square test with Yates' correction was used to compare complete response (CR) and relapse rates. Multivariate analysis using both the stepwise logistic-regression model and the Cox regression model was performed to determine independent prognostic variables. The factors studied included the clinical stage, serum lactate dehydrogenase level, sex, age, histological subtype, B symptoms, immunophenotype, primary site, number of extranodal sites, bulky disease and percentage of scheduled chemotherapy received.

Results

A total of 92 evaluable patients with intermediate- and high-grade NHL, including 52 (57%) men and 40 (43%) women, were investigated in this prospective study. Their median age was 48 years (range, 15–65 years). There were 2 (2%) cases of follicular large-cell lymphoma; 5 (5%) diffuse, small cleaved-cell lesions; 21 (23%) diffuse, mixed small- and large-cell lymphomas; 48 (52%) diffuse large-cell tumours; 9 (10%) diffuse large-cell immunoblastic lesions; 2 (2%) lymphoblastic lymphomas; 1 (1%) diffuse, small non-cleaved-cell lesions; and 5 (5%) unclassifiable lymphomas. B symptoms were observed in 29 (32%) patients and 19 (21%) had bulky disease (tumour diameter, >10 cm). Fresh tissue specimens were available for immunophenotyping in 76 (83%) cases. There were 22 (29%) T-cell and 54 (71%) B-cell lymphomas. The primary tumour sites were the lymph node in 46 (50%) cases, the gastrointestinal tract in 21 (23%) subjects, Waldeyer's ring and the nasal region in 10 (11%) patients, and other extranodal sites in the remaining 15 (16%) cases. The mean serum lactate dehydrogenase level was 412 μmol min^{-1} l (range, 256–1688 μmol min^{-1} l).

Each patient received 3–9 courses of m-BACOD chemotherapy, and additional radiotherapy was given to 32 (35%) subjects following the completion of chemotherapy. Myelosuppression was the major toxicity. A total of 20 (22%) patients had one or more episodes of neutropenic infection, including septicaemia and pneumonia, which proved fatal in 1 case. In 5 (5%) subjects, one or more episodes of serious but nonfatal bleeding were observed, 4 from the gastrointestinal tract and 1 from the nose, which were related to thrombocytopenia. All patients developed alopecia and experienced nausea and vomiting. Severe mucositis occurred in 5 (5%) cases, requiring the discontinuation of methotrexate. In all, 6 (7%) patients showed deterioration in their serial lung-function testing, and bleomycin was omitted from their subsequent courses. One patient died of malignant hyperpyrexia related to bleomycin during the second course of therapy.

Although all subjects were monitored by serial echocardiogram or isotope cardiac scan, 4 (4%) developed significant doxorubicin-related cardiotoxicity, which was fatal in 2 patients who had received cumulative doxorubicin doses of only 180 and 270 mg/m^2. Of 17 (18%) patients who were positive for hepatitis B surface antigen at the time of diagnosis, 5 exhibited reactivation of hepatitis in the form of elevated serum transaminase levels during therapy; 1 of them subsequently died of fulminating liver failure. In all, there were 5 (5%) treatment-related deaths. A proportion of the patients underwent significant treatment delays and dose reduction and/or drug omission due to treatment toxicities. The percentages of scheduled chemotherapy that were actually received by the patients were 91%–100% in 44 (48%) cases, 81%–90% in 26 (29%) subjects, 71%–80% in 7 (8%) patients, 61%–70% in 5 (5%) cases, 51%–60% in 8 (9%) subjects and 40%–50% in 2 (2%) cases.

The median follow-up period was 32 months (range, 1–67 months). The overall CR rate was 65/92 (71%) and the relapse rate was 22/65 (34%). The DFS of the 65 CR patients at 2 years was 52%, and the overall survival of all 92 patients at 3 years was 56%. Table 1 shows the treatment results according to the clinical stage of the patients. The CR rate of stage I and II patients was significantly better than that of subjects with stage III and IV disease (87% vs 59%; $P=0.01$), and the CR rate of stage III patients was significantly better than that of subjects with stage IV disease (86% vs 50%; $P=0.05$). The relapse rate and the DFS of CR patients were not significantly affected by clinical stage; however, the overall survival of stage III and IV patients was significantly worse than that of sub-

jects with stage I and II disease (31% vs 73%; $P=0.02$; Fig. 1).

Multivariate analysis revealed that the independent prognostic variables significantly determining the CR rate and survival included the clinical stage ($P=0.04$) and the serum lactate dehydrogenase level ($P=0.001$). Other variables, including sex, age, histological subtype, B symptoms, immunphenotype, primary site, number of extranodal sites, bulky disease and percentage of scheduled chemotherapy received, were not statistically significant.

Discussion

It has been shown that patients with intermediate- and high-grade NHL are curable; a plateau in the survival curve can be achieved by treating these patients with a combination chemotherapy regimen such as CHOP [1, 10, 11]. Early results suggest that the clinical outcome can be further improved by using the newer generation of chemotherapy regimens [1, 2, 10, 14]. The m-BACOD regimen incorporates six active agents, and the use of folinic acid rescue has enabled the administration of methotrexate at higher doses. Previous studies using this regimen in patients with diffuse large-cell lymphoma have shown a CR rate of 68%, a relapse rate of 25% and a plateau in the survival curve at 60% [2, 14].

We report herein our experience with this regimen in the treatment of a selected group of patients with intermediate- and high-grade grade NHL. The present study included patients who had all stages of the disease. Our overall treatment results were comparable with those reported previously, with patients showing a CR rate of 71%, a relapse rate of 34% and an overall survival of 56% at 5 years. However, when the patients were stratified according to clinical stages, it became apparent that those with advanced disease had a significantly worse prognosis. Stage III and IV patients achieved a CR rate of only 59% and their 3-year survival was only 31%; this finding is similar to the results previously obtained using the CHOP regimen [1, 9–11].

Treatment toxicities were not uncommon in our patients. Myelosuppression was the major side effect. Despite careful patient selection before therapy and monitoring of subjects, treatment-related mortality was 5%. Some degree of treatment delay and dose reduction and/or drug omission due to treatment toxicity was unavoidable in most patients.

The clinical stage and the serum lactate dehydrogenase level were found to be significant independent factors predicting prognosis. The inclusion of only patients who were <65 years of age, the small number of subjects with high-grade histology and the use of local therapy in patients with bulky disease might explain why age, histological subtype and bulky disease were not independent prognostic factors. It has been reported that the T-immunophenotype carries a poorer prognosis, but this was not substantiated in the present study [8]. The actual dose intensity of the chemotherapy delivered to patients has also been shown to be important for the efficacy of treatment, but the percentage of scheduled m-BACOD chemotherapy actually received did not turn out to be a significant independent prognostic factor in our patients [1, 10].

Previous studies of newer, intensive chemotherapy regimens, including m-BACOD, suggest that a CR is achieved in about two-thirds of the patients, and the long-term DFS is estimated to be attained by 50%–60% of all patients. However, when compared with existing data on the CHOP regimen, experience with the newer regimens has been relatively brief. The dramatic results obtained using many of these combinations may be modified with time by a decrease in the CR rate, DFS and overall survival. This may be attributable to the initial selection of good-risk patients, such as those with stage I and II disease and normal serum lactate dehydrogenase levels. Also, late relapses may occur. It remains unclear as to whether the CHOP regimen is inferior to the newer combinations, including m-BACOD. Prospective, comparative studies incorporating proper stratification of the various important prognostic factors are essential and some are under way. Preliminary results of the phase III study of the Southwest Oncology Group [4] have not yet demonstrated any superiority of m-BACOD over CHOP.

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