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# MACOP-B REGIMEN IN NON-HODGKIN'S LYMPHOMA

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**Two university centers in Finland used MACOP-B regimen as first-line treatment of intermediate and high-grade non-Hodgkin's lymphomas in 1986–1990. The clinical records of all 41 patients treated with this regimen were analyzed. The median age was 47 years (range 16–65), 24% of the patients had WHO performance status >1, 49% had B-symptoms, 46% had Ann Arbor stage III or IV disease, and 39% had bulky disease. Twenty-three (58%) of the 40 patients who were evaluable for response had CR. The survival rate 36 months after the start of MACOP-B was 62%, but failure-free survival rate only 36%. Among several analyzed factors a lactate dehydrogenase level <500 U/l before treatment showed the strongest association to failure-free survival. The planned dose intensity was not achieved mainly because of toxicity, and the ratio of the actual dose intensity given to the planned dose intensity varied for the different drugs between 0.77 and 0.92.**

MACOP-B regimen is a high-dose intensity regimen for non-Hodgkin's lymphoma introduced by Klimo & Connors in 1985 (1). All chemotherapy in this regimen is given within 12 weeks with myelosuppressive drugs (doxorubicin, cyclophosphamide) administered during the odd-numbered weeks alternating with non-cross-resistant, non-myelosuppressive drugs (bleomycin, vincristine, methotrexate) during the even-numbered weeks. In addition, prednisone in a fairly high dose is given for 12 weeks together with cotrimoxazole to prevent Pneumocystis carinii infection. Hence, the tumor cells are within a short time period exposed to several cytostatics, which should maximize response according to the somatic mutation hypothesis (2). Indeed, a high response rate (84% CR) and an 8-year failure-free survival rate of 52% were obtained by the designers of the regimen among patients with advanced diffuse large cell lymphoma (3). However, less promising results have recently been reported (4–6).

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The regimen has been used in 2 of the 5 university hospitals in Finland since 1986, and the present report includes all patients who received MACOP-B as first-line therapy for non-Hodgkin's lymphoma in these centers.

## Material and Methods

*Patients.* Forty-one patients with histologically verified and previously untreated intermediate or high-grade malignant non-Hodgkin's lymphoma were treated with MACOP-B as first-line therapy in the University Central Hospitals of Turku (n = 31) and Oulu (n = 10) in 1986–1990. The patients were not consecutive, but the regimen was the most commonly used for intermediate and high-grade malignant lymphomas according to the modified Kiel classification. Patient characteristics are shown in Table 1. None of the patients had AIDS, but HIV-testing was not routinely performed. Staging examinations included bone marrow biopsy, and the abdomen was investigated by computed tomography and/or ultrasound. Laparotomy had occasionally (in 34%) been performed. Remission was confirmed by repeating the staging examinations which initially had shown abnormal findings, and whenever appropriate, with histological or cytological examination. The median follow-up of the patients alive was 26 months (mean 28 months, range 4-57) from the start of MACOP-B therapy.

**Table 1**

*Patient characteristics*

| Characteristic | n (%) |
|---|---|
| Sex | |
| Male | 26 (63) |
| Female | 15 (37) |
| Median age (range) 47 yr (16–65 yrs) | |
| Performance status (WHO) | |
| 0 | 9 (22) |
| 1 | 22 (54) |
| 2 | 7 (17) |
| 3 | 2 (5) |
| 4 | 1 (2) |
| Histology | |
| Centrocytic-centroblastic | 9 (22) |
| Immunoblastic | 9 (22) |
| Centroblastic | 7 (17) |
| Centrocytic | 4 (10) |
| Peripheral T cell | 3 (7) |
| Lymphoblastic | 3 (7) |
| Large cell anaplastic (Ki-1) | 2 (5) |
| Unclassified | 4 (10) |
| Stage | |
| I | 10 (24) |
| II | 12 (29) |
| III | 7 (17) |
| IV | 12 (29) |
| B-symptoms | |
| No | 21 (51) |
| Yes | 20 (49) |
| Bulky mass (>10 cm) | |
| No | 25 (61) |
| Yes | 16 (39) |
| LDH | |
| <500 U/l | 20 (49) |
| >500 U/l | 15 (37) |
| Unknown | 6 (15) |

*Chemotherapy.* MACOP-B was given according to Klimo & Connors (1) with slight modifications. Methotrexate 400 mg/m$^2$ was given i.v. on weeks 2, 6, and 10 with leucovorin 15 mg orally every 6 h for 8 doses commencing 24 h after the start of the methotrexate infusion; doxorubicin 50 mg/m$^2$ i.v. (epirubicin 50 mg/m$^2$ in Oulu) and cyclophosphamide 350 mg/m$^2$ i.v. both given on weeks 1, 3, 5, 7, 9, and 11; vincristine 1.4 mg/m$^2$ i.v. (maximum dose 2 mg) on weeks 2, 4, 6, 8, 10, and 12; and bleomycin 10 mg/m$^2$ i.v. on weeks 4, 8, and 12. Of methotrexate, 100 mg/m$^2$ was given as bolus, and the remaining 300 mg/m$^2$ as infusion over 4 h. Bleomycin was infused over at least 15 min. Prednisone 75 mg was given orally daily for the entire course of 12 weeks (tapered during weeks 11 and 12), except for 16 patients who received the lower starting dose of 60 mg. Trimethoprim 160 mg and sulfamethoxazole 800 mg were given orally twice daily throughout the treatment. Other medication given occasionally included allopurinol, ketoconazole, ranitidine, and antiemetics. Response to treatment was assessed as reported by Miller et al. (7). Radiotherapy 30 to 40 Gy was given to involved regions with residual disease or to establish complete remission (CR) in 23 patients. Two patients received <20 Gy.

*Dose intensity and statistical analysis.* Dose intensity was calculated according to principles by Hryniuk & Bush (8) and Weick et al. (6). For each agent, dose intensity was calculated for 3 consecutive 4-week periods after start of treatment as mg/m$^2$/week. Actual dose intensity was calculated as follows: Let $n_1$ be the number of patients alive without progression at the start of the first week of therapy. Let $d_1$ be the total dose per square meter delivered to all $n_1$ patients during the first week. Since a cycle of therapy is 4 weeks long, the dose intensity for the first 4 weeks of therapy is $(d_1 + d_2 + d_3 + d_4)/(4 \times n_1)$. The dose intensity for weeks 5 to 8 is $(d_5 + d_6 + d_7 + d_8)/(4 \times n_5)$. The average dose intensity over the first 12 weeks of therapy is $(d_1 + d_2 + \cdots + d_{12})/(4 \times (n_1 + n_5 + n_9))$. Patients who died, progressed, or for other reasons ceased to receive MACOP-B therapy during the 4-week interval were included when calculating the dose intensity of the interval, but were excluded from the denominator when calculating dose intensity of the subsequent intervals. Patients who had therapy temporarily interrupted because of toxicity were included in the dose intensity calculations, and were considered to have zero dose intensity at the time of interruption. The planned dose intensity was calculated from the protocol, assuming no dose reductions or delays. The planned dose for vincristine was 1 mg/wk for all except one of the patients, since a 2 mg upper limit for the dose was used for patients with a surface area larger than 1.43 m$^2$. Relative dose intensity was calculated as the ratio between the actual and the planned dose intensity.

Survival analyses were made using a BMDP computer program (BMDP Statistical Software, Department of Biomathematics, University of California Press, Los Angeles, CA). Survival was estimated with the product-limit method, and comparison of survival between groups was made with the generalized Wilcoxon's test (BMDP 1L). Survival duration was measured from the date of starting MACOP-B to the date of death or last follow-up, and time to treatment failure ('failure-free survival') to the date of disease progression, relapse, death, or last follow-up.

## Results

Complete response (CR) was observed in 23 (58%) patients, partial response (PR) in 15 (38%), and progressive disease in 2 (5%) of the 40 patients who were evaluable for response after MACOP-B treatment. Twelve of the 15 PRs could be converted into CR by involved field radiotherapy, and one by radiotherapy and the ABVD regimen. Thus, 36 of the evaluable 40 patients (90%) were considered to be in CR after the primary treatment. In 6 cases more that 12 weeks of active chemotherapy with the

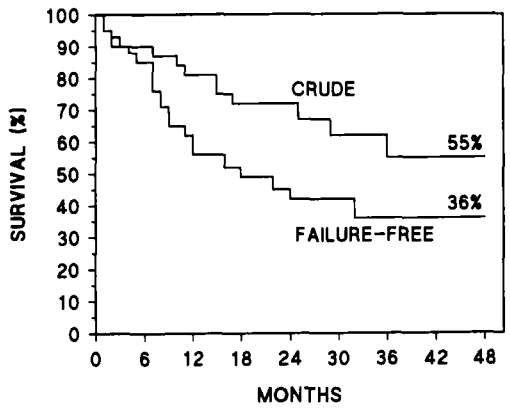


*Figure.* Survival and failure-free survival among 41 patients with non-Hodgkin's lymphoma treated with MACOP-B.

MACOP-B regimen was given due to inability to achieve CR with 12 weeks of chemotherapy (n = 5) or due to dose reduction (n = 1). MACOP-B therapy was interrupted before 12 weeks in 10 cases either due to progressive disease (n = 2) or toxicity (infection, n = 4; exhaustion and patient refusal, n = 1; attempted suicide, n = 1; suicide, n = 1; toxic death, n = 1).

The crude survival rate at 2 years after starting therapy was 72%, and at 3 years 62% (Figure). The failure-free survival rate was only 45% at 2 and 36% at 3 years after starting therapy respectively. The 3-year failure-free survival rate of the 23 patients who achieved CR by MACOP-B alone was 49%.

Patients with a low serum LDH level ( < 500 U/l, the most effective cut-off level, n = 19) had 53% 3-year failure-free survival rate, whereas none of the patients with a high LDH level ( > 500 U/l, n = 15) survived longer than for 24 months (p = 0.002). Patients with stage I or II disease had a 59% failure-free 3-year survival rate, while that of the patients with stage III or IV lymphoma was only 16% (p = 0.02). Good performance status (WHO 0 or 1) and young age ( < 40) also tended to be associated with favorable failure-free survival (p = 0.07 and 0.09 respectively), but no significant difference could be found by sex, histological grade (high grade vs. intermediate grade), tumor bulk (bulky vs. non-bulky), presence of B-symptoms, or by hospital.

The recorded toxicity is shown in Tables 2 and 3. Although hematological toxicity was only moderate, MACOP-B treatment caused considerable toxicity. The majority of patients had mucositis (73%), which was severe in 23%. Peripheral neurotoxicity was also common (76%), and grade 3 neurotoxicity was present in 18% of the patients. Severe fatigue, exhaustion, and weight gain were also common. Two patients attempted suicide during the treatment, one of the attempts led to death, and a third patient with a previous liver disease died from progressing liver failure during treatment. One patient had myocardial infraction 19 days after the last dose of chemotherapy.

**Table 2**

*Hematologic toxicity*

| Nadir values | n % |
|---|---|
| WBC ( $\times 10^9$/l) | |
| >4.0 | 9 (23) |
| 3.0–3.9 | 6 (15) |
| 2.0–2.9 | 8 (20) |
| 1.0–1.9 | 12 (30) |
| <1.0 | 5 (13) |
| Hemoglobin (g/l) | |
| >110 | 14 (35) |
| 95–109 | 14 (35) |
| 80–94 | 11 (28) |
| 65–79 | 1 (3) |
| Platelets ( $\times 10^9$/l) | |
| >100 | 37 (93) |
| 75–99 | 0 (0) |
| 50–74 | 2 (5) |
| 25–49 | 0 (0) |
| <25 | 1 (3) |

The actually achieved dose intensity during the first 12 weeks of therapy was less than the planned one. The relative dose intensity varied from 0.77 (bleomycin) to 0.92 (methotrexate, Table 4). Thus, the high-dose intensity intended by the protocol could often not be achieved.

## Discussion

The 58% CR rate obtained in the present series is not very different from the rates found with MACOP-B in the Memorial Sloan-Kettering Cancer Center (MSKCC (5)), by the Southwest Oncology Group (SWOG (6)), and in the Italian multicenter study ((4) 54%, 50%, and 69% respectively), but somewhat lower than 84% reported by the Vancouver group (3). Three-year survival rates are available from the Vancouver, MSKCC, and the SWOG studies, and they are rather similar to the 62% found in the present series (67%, 56%, and 51% respectively). It should, however, be noted that, unlike the Vancouver series, the present series contained also 10 patients with stage I disease, and 5 of them were treated with local radiotherapy too, which may have influenced the survival rate.

The Vancouver group has reported an 8-year failure-free survival rate as high as 52% in diffuse large cell lymphoma, and the 3-year failure-free survival rate of 36% obtained by us may seem somewhat disappointing. The SWOG has also published their 3-year failure-free survival rate, which was similar to the rate found in the present series, 42%. The SWOG group is also the only one that has calculated relative dose intensity of the drugs given. Their relative dose intensities for cyclophosphamide, doxorubicin, bleomycin, methotrexate, and vincristine were 0.89, 0.88, 0.76, 0.92 and 0.84 respectively, figures very similar to ours (Table 4). Hence, it appears that the MACOP-B regimen may be difficult to deliver at the planned dose intensity.

**Table 3**

*Non-hematological toxicity*

| | n (%) |
|---|---|
| Gastrointestinal | |
| Mucositis, stomatitis, candidiasis (grade 3 to 4, 9/40) | 29 (73) |
| Nausea, vomiting | 14 (35) |
| Epigastric pain, gastritis, ulcer, GI bleed | 10 (25) |
| Constipation | 5 (13) |
| Diarrhea | 2 (5) |
| Pyrosis | 2 (5) |
| Dysphagia | 1 (3) |
| Neurologic | |
| Paresthesias (WHO grade 1) | 12 (30) |
| Muscle weakness (WHO grade 2) | 11 (28) |
| Paresis (WHO grade 3) | 7 (18) |
| Joint/muscle pain | 8 (20) |
| Back ache | 5 (13) |
| Tremor | 2 (5) |
| Other | 5 (13) |
| Psychiatric | |
| Attempted suicide | 2 (5) |
| Depression | 2 (5) |
| Other | 4 (10) |
| Dermatologic/Eyes | |
| Alopecia | 22 (55) |
| Conjunctivitis/lacrimation/eye ache | 9 (23) |
| Loss of nails | 3 (8) |
| Hyperpigmentation/inflammation | 3 (8) |
| Blisters | 2 (5) |
| Itching | 1 (3) |
| Infectious | |
| Septicemia | 6 (15) |
| Herpes infection | 6 (15) |
| Pneumonia | 1 (3) |
| Other (mild) | 22 (55) |
| Endocrine | |
| Hypothyreosis | 1 (3) |
| Hyperglycemia | 1 (3) |
| General | |
| Fatigue/exhaustion | 15 (38) |
| Weight gain/edema | 14 (35) |
| Loss of weight (>5 kg) | 2 (5) |
| Miscellaneous | |
| Toxic death (suspected) | 1 (3) |
| Myocardial infarction | 1 (3) |
| Other (mild) | 8 (20) |

**Table 4**

*Dose intensity for MACOP-B*

| Drug | Actual dose intensity given ($mg/m^2/wk$) | Planned dose intensity ($mg/m^2/wk$) | Relative dose intensity |
|---|---|---|---|
| Cyclophosphamide | 151 | 175 | 0.86 |
| Doxorubicin | 21.2 | 25 | 0.85 |
| Bleomycin | 1.92 | 2.50 | 0.77 |
| Methotrexate | 92.3 | 100 | 0.92 |
| Vincristine | 0.81 mg/wk | 1 mg/wk | 0.81 |

Bone marrow growth stimulating factors were not used in the present study.

Toxicity commonly involved mucositis and neuropathy. To reduce mucositis and to facilitate the delivery of the regimen, the Vancouver group has now replaced methotrexate by etoposide (3). The high cortisone dose for 12 weeks may also cause side-effects, such as weight gain, epigastric pain, and Cushing habitus, as well as emotional changes, and it may have contributed to the two attempts of suicide seen in the present series. The frequency of treatment-related deaths was 5%, which is compatible with previous reports, where toxic deaths have been seen in 5 to 10% of the cases (3–6).

The present results and those obtained by SWOG and MSKCC do not provide firm evidence that the MACOP-B regimen leads to superior survival rates when compared with CHOP chemotherapy, which results in 25 to 35% disease-free survival at 10 years after therapy (9). However, a dose-intensive third generation regimen ProMACE–CytaBOM has recently in a randomized study been shown to improve survival when compared with a second generation regimen ProMACE-MOPP (10), and another randomized study showed that the addition of bleomycin and vincristine at mid-interval (d. 15) of a CHOP-like first generation regimen CHVmP (cyclophosphamide, doxorubicin, VM-26, and prednisone) resulted in a better outcome (11). A feasible and well-tolerated way to combine active drugs with low myelotoxicity, such as bleomycin, vincristine and methotrexate, with more myelotoxic drugs may be an important reason for these results. Results from ongoing randomized trials comparing MACOP-B with less intensive regimens are awaited with interest.

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