

COMPARISON OF A STANDARD REGIMEN (CHOP) WITH THREE INTENSIVE CHEMOTHERAPY REGIMENS FOR ADVANCED NON-HODGKIN'S LYMPHOMA

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Abstract Background. CHOP is a first-generation, combination-chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone that has cured approximately 30 percent of patients with advanced stages of intermediate-grade or high-grade non-Hodgkin's lymphoma in national cooperative-group trials. However, studies at single institutions have suggested that 55 to 65 percent of such patients might be cured by third-generation regimens such as ones consisting of low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM); and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B).

Methods. To make a valid comparison of these regimens, the Southwest Oncology Group and the Eastern Cooperative Oncology Group initiated a prospective, randomized phase III trial. The study end points were the response rate, time to treatment failure, overall survival, and incidence of severe or life-threatening

toxicity. Dose intensity was calculated and analyzed.

Results. Of the 1138 patients registered for the trial, 899 were eligible. Each treatment group contained at least 218 patients. Known prognostic factors were equally distributed among the groups. There were no significant differences among the groups in the rates of partial and complete response. At three years, 44 percent of all patients were alive without disease; there were no significant differences between the groups (41 percent in the CHOP and MACOP-B groups and 46 percent in the m-BACOD and ProMACE-CytaBOM groups; $P = 0.35$). Overall survival at three years was 52 percent (50 percent in the ProMACE-CytaBOM and MACOP-B groups, 52 percent in the m-BACOD group, and 54 percent in the CHOP group; $P = 0.90$). There was no subgroup of patients in which survival was improved by a third-generation regimen. Fatal toxic reactions occurred in 1 percent of the CHOP group, 3 percent of the ProMACE-CytaBOM group, 5 percent of the m-BACOD group, and 6 percent of the MACOP-B group ($P = 0.09$).

Conclusions. CHOP remains the best available treatment for patients with advanced-stage intermediate-grade or high-grade non-Hodgkin's lymphoma. (N Engl J Med 1993;328:1002-6.)

THE development of curative combination chemotherapy for patients with advanced stages of aggressive non-Hodgkin's lymphoma has been one of the major successes of cancer therapy during the past two decades. First-generation regimens, which generally included four chemotherapeutic agents, produced complete remission in 45 to 55 percent of patients and cure in approximately 30 to 35 percent.¹⁻⁵ Among these first-generation regimens, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was studied extensively in national cooperative-group trials and has been considered standard therapy. In the 1980s, several large lymphoma-referral centers conducted pilot trials of second-generation and third-generation treatment programs that used six to eight chemotherapeutic drugs.⁶ These third-generation regimens included ones consisting of methotrex-

ate in a low dose with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD)⁷; prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM)⁸; and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B).⁹ Initially increased rates of complete remission and survival rates of 55 to 65 percent were reported, but follow-up was limited and these new treatment programs were more difficult to administer, more toxic, and more costly.

Therefore, in April 1986 the Southwest Oncology Group initiated a phase III comparison of CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B for the treatment of patients with intermediate-grade or high-grade non-Hodgkin's lymphoma, in order to evaluate in a randomized setting the response rate, time to treatment failure, survival, and toxicity of standard chemotherapy — i.e., to compare CHOP with the third-generation regimens. The Eastern Cooperative Oncology Group joined the study on January 15, 1988, and the trial was designated the National High Priority Lymphoma Study by the National Cancer Institute on November 14, 1988.

METHODS

Treatment Protocol

Patients were eligible if they had measurable, biopsy-confirmed

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or high-grade disorder other than lymphoblastic lymphoma (i.e., patients in working formulation groups D through H and group J).¹⁰ There were no age restrictions. Patients were excluded if they had any of the following: previous treatment with chemotherapy or radiotherapy; lymphoma associated with the acquired immunodeficiency syndrome; a history of low-grade lymphoma; a history of neoplasm; overt central nervous system disease; marked impairment of cardiac function, indicated by an abnormal result on multiple-gated acquisition scanning in patients with a history of such impairment; a carbon monoxide-diffusing capacity below 50 percent; or a serum creatinine concentration of 1.7 mg per deciliter (150 μ mol per liter) or more and a calculated serum creatinine clearance of 60 ml per minute or less. All patients gave written informed consent.

Randomization was stratified according to five factors: bone marrow infiltration (present vs. absent); bulky disease (present vs. absent), indicated by a mediastinal mass that was greater than one third of the maximal diameter of the chest or any mass more than 10 cm in diameter; age (<65 vs. \geq 65 years); lactate dehydrogenase concentration (\leq 250 vs. >250 U per liter); and working formulation group (group D or E vs. group F, G, or H vs. group J).¹⁰

All chemotherapy was administered exactly as described in the original reports of the regimens.^{5,7,9,11} CHOP was given in eight consecutive 21-day courses unless progressive disease developed. Central nervous system prophylaxis was carried out in the ProMACE-CytaBOM and MACOP-B groups, as was initially recommended, but not in the CHOP and m-BACOD groups. Vincristine doses did not exceed 2.0 mg in the m-BACOD group. Modification of dosages because of hematologic or other toxicity was based on precise guidelines in the initial reports.^{7,9,11}

All patients underwent repeat staging after therapy ended. Complete remission has traditionally been defined as the disappearance of all clinical evidence of active tumor for a minimum of four weeks; remission is verified by repeating all radiographic tests previously yielding positive findings. With the advent of modern radiographic techniques such as computed tomography and magnetic resonance imaging, residual abnormalities of various sizes have frequently been detectable after treatment, making an accurate assessment of complete responses very difficult. Therefore, in this study the rate of complete response was estimated conservatively: no peripheral disease could be present, and any abnormalities detected on abdominal or chest radiography had to be less than 2.5 cm in diameter. A partial remission was indicated by a decrease of more than 50 percent in the sum of the products of the maximal perpendicular diameters of the measured lesions, lasting at least four weeks. Disease progression was indicated by the appearance of new lesions or by a 25 percent increase in the size of preexisting lesions.

Statistical Analysis

All eligible patients were included in the comparisons of the treatment groups. The patients' characteristics, responses, and toxic reactions were compared by chi-square tests. The time to treatment failure was measured from the date of randomization to disease progression, relapse, or death. Only the data on patients alive without disease were censored at the time of the last contact. Survival was measured from the date of randomization to death (from any cause) or the date of the last contact. Only the data on patients known to be alive at the most recent follow-up visit were censored in the survival analysis. The rates of treatment failure and survival were estimated according to the method of Kaplan and Meier.¹² The treatment groups were compared by log-rank tests¹³ and Cox partial-likelihood-score tests.¹⁴ Relative risks were estimated with the Cox regression model.¹⁵ All tests for significance were two-sided and were not adjusted for multiple comparisons (except where indicated in this report).

Characteristics of the Treatment Groups

Between April 4, 1986, and June 15, 1991, 1138 patients were registered for the study. Thus, the median follow-up period was 35 months, and the maximal follow-up period was 6 years. Two hundred thirty-nine patients were ineligible primarily because their

tory review of the pathological findings. Frequently, their biopsy specimens had both follicular and diffuse components, indicating that the histologic character of some tumors had been transformed, producing more aggressive disease. However, the working formulation¹⁰ defines a lymphoma as low grade if it contains any residual follicular component. Thus, 899 patients were eligible, with 225 in the CHOP group, 223 in the m-BACOD group, 233 in the ProMACE-CytaBOM group, and 218 in the MACOP-B group. The characteristics of these patients are shown in Table 1. The median ages of the groups ranged from 54 to 57 years; the youngest patient was 15 years old, and the oldest 81. Approximately one fourth of the patients studied were 65 years of age or older. Bone marrow involvement was present in approximately 25 percent of patients, bulky disease in approximately 40 percent, and high concentrations of lactate dehydrogenase in approximately 45 percent. Approximately 80 percent of the patients were classified as belonging to working formulation¹⁰ group F, G, or H. There were no differences among the four treatment groups in these important prognostic factors.

RESULTS

Response to Treatment

The rates of objective antitumor responses were 80 percent in the CHOP group, 82 percent in the m-BACOD group, 83 percent in the MACOP-B group, and 87 percent in the ProMACE-CytaBOM

Table 1. Characteristics of the Patients, According to Chemotherapeutic Regimen.

CHARACTERISTIC	CHOP (N = 225)	m-BACOD (N = 223)	ProMACE- CytaBOM (N = 233)	MACOP-B (N = 218)
Age				
Median (yr)	56	57	54	57
Range (yr)	15-79	18-81	17-81	19-79
\geq 65 yr (%)	26	25	27	24
Marrow involvement (%)	25	26	27	27
Bulky disease (%)	40	41	41	40
LDH >250 U/liter (%)*	45	43	42	43
Working formulation group (%)†				
D or E	14	15	15	14
F, G, or H	81	82	81	82
J	5	4	4	4

*LDH denotes lactate dehydrogenase.

†These groups were defined according to the system of the Non-Hodgkin's Lymphoma Pathologic Classification Project.¹⁰

group. The rates of complete responses as defined above were 44 percent for CHOP, 48 percent for m-BACOD, 56 percent for ProMACE-CytaBOM, and 51 percent for MACOP-B; the rates of partial responses were 36 percent for CHOP, 34 percent for m-BACOD, 31 percent for ProMACE-CytaBOM, and 32 percent for MACOP-B. There were no significant differences between the treatment groups in the rates of objective, partial, or complete responses.

Because of the difficulty in assessing complete responses, the curves for the time to treatment failure provide a more accurate estimate of the fraction of patients who were cured by their initial treatment. Of all 899 patients, 44 percent were estimated to be alive without disease after three years. As shown in Figure 1, the percentage of patients alive without disease at three years was estimated to be 41 percent in the CHOP and MACOP-B groups and

BOM groups. The differences in disease-free survival were not significant ($P = 0.35$).

Overall Survival

Fifty-two percent of the 899 patients were estimated to be alive at three years. Overall survival was analyzed according to the treatment group assigned at randomization (Fig. 2). At three years, the estimated overall survival was 50 percent in both the ProMACE-CytaBOM and the MACOP-B groups, 52 percent in the m-BACOD group, and 54 percent in the CHOP group. The differences in overall survival were also not significant ($P = 0.90$).

Dose Intensity

Because the results of therapy may be affected by the doses of chemotherapeutic agents actually administered, dose intensity was calculated for all patients in this study. Unfortunately, comparable data were not available from the initial trials of m-BACOD⁷ and MACOP-B,⁹ but they were available from a trial of ProMACE-CytaBOM.¹¹ When the dose intensity of ProMACE-CytaBOM in this study was compared with that in the study of Longo et al., according to their definition of dose intensity,¹¹ the data were comparable (Table 2). The dose intensities of the three third-generation regimens in this study were also comparable to the intensities of these regimens in the initial phase II trials of the Southwest Oncology Group.¹⁶⁻¹⁸

Toxicity

The toxic reactions observed in this clinical trial were similar to those reported in phase II trials of the same regimens.^{7,9,11} The severe reactions were caused by granulocytopenia and subsequent infection. The incidence of grade 5, or fatal, toxicity was 1 percent in the CHOP group, 3 percent in the ProMACE-CytaBOM group, 5 percent in the m-BACOD group, and 6 percent in the MACOP-B group. The differences

between these rates were not significant ($P = 0.09$). Grade 4, or life-threatening, toxicity occurred in 31 percent of patients in the CHOP group, 54 percent in the m-BACOD group, 29 percent in the ProMACE-CytaBOM group, and 43 percent in the MACOP-B group. When the fatal and life-threatening reactions were combined (i.e., grade 5 plus grade 4 reactions), significant differences were found between the regimens ($P = 0.001$), with CHOP and ProMACE-CytaBOM being less toxic than m-BACOD and MACOP-B.

Subgroup Analysis

When the patients were evaluated according to important prognostic factors,^{7,19-23} we found no subgroups in which the third-generation regimens significantly increased either the time to treatment failure or survival. A predictive model for aggressive lymphomas has been presented by the International Non-Hodgkin's Lymphoma Prognostic Factors Project.²⁴ Five factors were independently associated with poor survival: age of more than 60 years, stage III or IV disease, disease at two or more extranodal sites, poor performance status, and abnormal serum lactate dehydrogenase levels. Patients were categorized as being at low, low-to-intermediate, intermediate-to-high, or high risk on the basis of the number of unfavorable risk factors present: patients with no risk factors or one risk factor were considered to be at low risk, those with two factors were at low-to-intermediate risk, those with three factors were at intermediate-to-high risk, and those with four or five factors were at high risk. When the patients were divided into these four risk groups and the time to treatment failure and overall survival were analyzed according to regimen, there was no significant difference between any of the regimens in any of the risk groups (data not shown).

DISCUSSION

CHOP, the most commonly used first-generation chemotherapy regimen, cures a subgroup of patients with advanced stages of aggressive non-Hodgkin's lymphomas. Among 418 patients treated in three consecutive national phase III studies, the rate of complete remission was 53 percent and the survival rate was 30 percent after 12 years of follow-up.⁵ In the past decade, several large lymphoma-referral centers have developed second-generation and third-generation regimens by incorporating additional chemotherapeutic drugs into treatment programs.^{7,9,11,25-27} Initially, each of these centers reported complete-remission rates of 70 to 85 percent and predicted long-term survival of 55 to 65 percent.

Although studies of third-generation regimens concluded that they improved survival substantially as compared with standard CHOP, for several reasons these pilot studies were probably insufficient to reach that conclusion. First, the studies at single institutions compared their current results with historical data from cooperative-group studies even though the study populations were not homogeneous and multiple im-

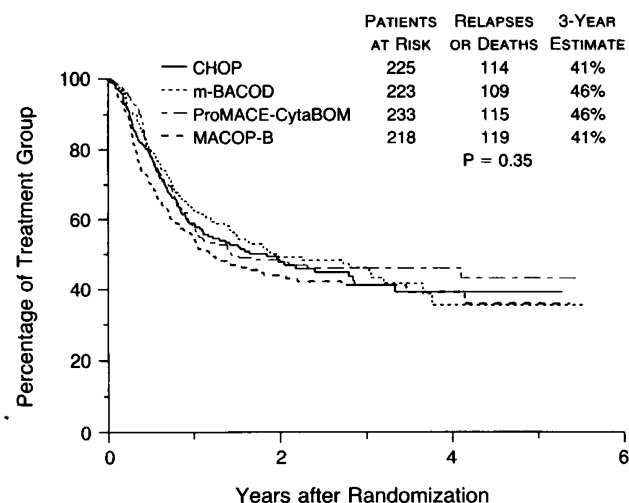


Figure 1. Time to Treatment Failure in the Treatment Groups.

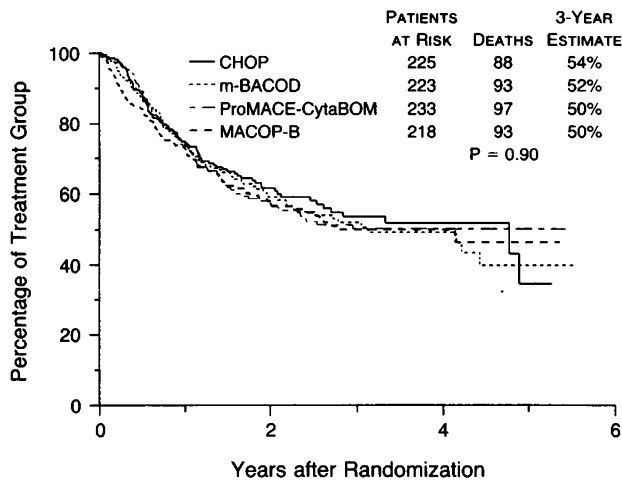


Figure 2. Overall Survival in the Treatment Groups.
The three-year estimate is of overall survival.

portant prognostic factors defined subgroups of patients with different responses to chemotherapy and thus markedly different survival.^{3,19-21} Second, in the studies at single institutions, the follow-up periods were relatively short and longer follow-up demonstrated an increase in late relapses and deaths occurring after two years.^{7,11,25,26,28} For example, the projected five-year survival rate for both m-BACOD and M-BACOD (a regimen like m-BACOD except that methotrexate is given in a high dose) is now 54 percent,⁷ much lower than the initially projected rate of 64 percent.²⁶ Long-term survival after treatment with a combination of prednisone, methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine (ProMACE-MOPP)²⁵ fell from 65 percent to 50 percent after nine years of follow-up.¹¹ Survival among patients treated with MACOP-B,⁹ initially 76 percent, subsequently fell to 65 percent.²⁸ Third, subsequent phase II trials of these third-generation regimens conducted by other single institutions and cooperative groups have reported lower rates of complete remission and survival.^{16-18,29} For example, a series of phase II trials confirmed the activity of m-BACOD, ProMACE-CytaBOM, and MACOP-B,^{16-18,30} but in each case the rates of complete remission (50 to 65 percent) and projected early survival were lower than previously reported.

In this study — a phase III comparison of CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B for the treatment of intermediate-grade or high-grade non-Hodgkin's lymphoma — the four treatment groups were well balanced with respect to prognostic factors. There were no significant differences in the rates of objective, partial, or complete responses, the curves for the time to treatment failure (41 percent of patients in the CHOP and MACOP-B groups were alive without disease at three years, and 46 percent in the m-BACOD and ProMACE-CytaBOM groups), or the estimated overall survival (50 percent at three years in the ProMACE-CytaBOM and MACOP-B

groups, 52 percent in the m-BACOD group, and 54 percent in the CHOP group). However, the incidence of serious toxicity did differ significantly among the groups. Fatal toxic reactions occurred in 1 percent of the CHOP group, 3 percent of the ProMACE-CytaBOM group, 5 percent of the m-BACOD group, and 6 percent of the MACOP-B group. When the fatal and life-threatening reactions were combined, significant differences were found between the groups ($P = 0.001$), with CHOP and ProMACE-CytaBOM being less toxic than m-BACOD and MACOP-B. The cost of the drugs in these treatment programs also varied considerably. If the cost of the drugs used in a planned course of CHOP is assigned a value of 1.00, the cost of MACOP-B is 1.13, that of ProMACE-CytaBOM 1.44, and that of m-BACOD 2.26 (on the basis of average wholesale prices³¹). Because overall survival and survival without treatment failure in the CHOP group were not significantly different from survival in the three other groups, and because the rate of severe toxic reactions and the cost of the CHOP regimen are lower, CHOP remains the best available treatment for patients with advanced-stage, intermediate-grade or high-grade non-Hodgkin's lymphoma.

The analysis of the results of this trial with respect to the important prognostic factors revealed no significant differences among the regimens. The dose intensity in the ProMACE-CytaBOM group was comparable to that previously reported by the National Cancer Institute,¹¹ and the dose intensity in the m-BACOD and MACOP-B groups was comparable to that previously reported in phase II trials of these regimens by the Southwest Oncology Group.^{7,9} The current study was designed to detect a 15 percent difference between CHOP and the third-generation regimens in the treatment-failure rates. With the current follow-up, the relative risk of treatment failure with the third-generation regimens as compared with CHOP is 0.87 for m-BACOD (95 percent confidence interval, 0.67 to 1.15), 0.91 for ProMACE-CytaBOM (95 percent confidence interval, 0.70 to 1.14), and 1.16 for MACOP-B (95 percent confidence interval, 0.89 to 1.51). The hypothesized 15 percent difference in risk corresponds to a relative risk of 0.67. At the final planned interim analysis, the null hypothesis that there was at least a 15 percent improvement in the

Table 2. Dose Intensity of the First Six Courses of ProMACE-CytaBOM in the Present Study and the Study by Longo et al.¹¹

AGENT	PRESENT STUDY	LONGO ET AL.
	<i>mg/m²/wk</i>	
Cyclophosphamide	176.1	175.1
Doxorubicin	6.7	6.7
Vincristine	0.36	0.41
Methotrexate	34.1	35.4
Bleomycin	1.44	1.44
Cytarabine	79.7	83.5
Etoposide	33.2	33.0

rate of treatment failure with the third-generation regimens as compared with the CHOP regimen was rejected (CHOP vs. m-BACOD, $P = 0.025$; CHOP vs. ProMACE-CytaBOM, $P = 0.01$; and CHOP vs. MACOP-B, $P = 0.001$, by one-sided tests). Thus, it is unlikely that additional follow-up will show that any of these third-generation regimens reduces the treatment-failure rate by 15 percent, as compared with CHOP. We will continue to follow these patients to detect smaller long-term differences.

There have been few published randomized comparisons of CHOP with the three most widely used third-generation regimens. A recent report found no significant difference in complete remission, time to treatment failure, or survival between CHOP and m-BACOD.³² Preliminary comparisons of CHOP with ProMACE-CytaBOM³³ and with MACOP-B³⁴ also found no significant differences. A new, aggressive chemotherapy regimen was shown to be superior to a modified first-generation program containing teniposide.³⁵ Other studies have compared various second-generation and third-generation regimens.^{8,11,36,37}

It appears unlikely that the use of different combinations of existing drugs will significantly improve the results of therapy. Innovative approaches are needed. The efficacy of any promising new treatment program will need to be assessed by comparing it with CHOP in randomized clinical trials.

REFERENCES

- DeVita VT Jr, Canellos GP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. *Lancet* 1975;1:248-50.
- Schein PS, DeVita VT Jr, Hubbard S, et al. Bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. *Ann Intern Med* 1976;85:417-22.
- Fisher RI, DeVita VT Jr, Johnson BL, Simon R, Young RC. Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Am J Med* 1977;63:177-82.
- Gaynor ER, Ultmann JE, Golomb HM, Sweet DL. Treatment of diffuse histiocytic lymphoma (DHL) with COMLA (cyclophosphamide, oncovin, methotrexate, leucovorin, cytosine arabinoside): a 10-year experience in a single institution. *J Clin Oncol* 1985;3:1596-604.
- Coltman CA, Dahlberg S, Jones SE, et al. Southwest Oncology Group studies in diffuse large cell lymphoma: a subset analysis. In: Kimura K, ed. *Cancer chemotherapy: challenges for the future*. Tokyo, Japan: Excerpta Medica, 1988:194-202.
- Coleman M. Chemotherapy for large-cell lymphoma: optimism and caution. *Ann Intern Med* 1985;103:140-2.
- Shipp MA, Harrington DP, Klatt MM, et al. Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. *Ann Intern Med* 1986;104:757-65.
- Fisher RI, DeVita VT Jr, Hubbard SM, et al. Randomized trial of ProMACE-MOPP vs. ProMACE-CytaBOM in previously untreated, advanced stage, diffuse aggressive lymphomas. *Proc Am Soc Clin Oncol* 1984;3:242.
- Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann Intern Med* 1985;102:596-602.
- The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112-35.
- Longo DL, DeVita VT Jr, Duffey PL, et al. Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. *J Clin Oncol* 1991;9:25-38. [Erratum, *J Clin Oncol* 1991;9:710.]
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
- Cox DR. Partial likelihood. *Biometrika* 1975;62:269-76.
- Idem*. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Dana BW, Dahlberg S, Miller TP, et al. m-BACOD treatment for intermediate- and high-grade malignant lymphomas: a Southwest Oncology Group phase II trial. *J Clin Oncol* 1990;8:1155-62.
- Miller TP, Dahlberg S, Weick JK, et al. Unfavorable histologies of non-Hodgkin's lymphoma treated with ProMACE-CytaBOM: a groupwise Southwest Oncology Group study. *J Clin Oncol* 1990;8:1951-8.
- Weick JK, Dahlberg S, Fisher RI, et al. Combination chemotherapy of intermediate-grade and high-grade non-Hodgkin's lymphoma with MACOP-B: a Southwest Oncology Group study. *J Clin Oncol* 1991;9:748-53.
- Fisher RI, Hubbard SM, DeVita VT Jr, et al. Factors predicting long-term survival in diffuse mixed, histiocytic, or undifferentiated lymphoma. *Blood* 1981;58:45-51.
- Dixon DO, Neilan B, Jones SE, et al. Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma: the Southwest Oncology Group experience. *J Clin Oncol* 1986;4:295-305.
- Jagannath S, Velasquez WS, Tucker SL, Manning JT, McLaughlin P, Fuller LM. Stage IV diffuse large-cell lymphoma: a long-term analysis. *J Clin Oncol* 1985;3:39-47.
- Coiffier B, Lepage E. Prognosis of aggressive lymphomas: a study of five prognostic models with patients included in LNH-84 regimen. *Blood* 1989;74:558-64.
- Danieu L, Wong G, Koziner B, Clarkson B. Predictive model for prognosis in advanced diffuse histiocytic lymphoma. *Cancer Res* 1986;46:5372-9.
- Shipp M, Harrington D, Anderson J, et al. Development of a predictive model for aggressive lymphomas: the international NHL Prognostic Factors Project. *Proc Am Soc Clin Oncol* 1992;11:319. abstract.
- Fisher RI, DeVita VT Jr, Hubbard SM, et al. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. *Ann Intern Med* 1983;98:304-9.
- Skarin AT, Canellos GP, Rosenthal DS, et al. Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). *J Clin Oncol* 1983;1:91-8.
- Laurence J, Coleman M, Allen SL, Silver RT, Pasmantier M. Combination chemotherapy of advanced diffuse histiocytic lymphoma with the six-drug COP-BLAM regimen. *Ann Intern Med* 1982;97:190-5.
- Connors JM, Klimo P. MACOP-B chemotherapy for malignant lymphomas and related conditions: 1987 update and additional observations. *Semin Hematol* 1988;25:Suppl 2:41-6.
- Schneider AM, Straus DJ, Schluger AE, et al. Treatment results with an aggressive chemotherapeutic regimen (MACOP-B) for intermediate- and some high-grade non-Hodgkin's lymphomas. *J Clin Oncol* 1990;8:94-102.
- Lowenthal DA, White A, Koziner B, Straus DJ, Lee BJ, Clarkson BD. MACOP-B for advanced diffuse intermediate and high grade non-Hodgkin's lymphoma (NHL): preliminary results of the Memorial Hospital experience. *Proc Am Soc Clin Oncol* 1987;6:201. abstract.
- Drug topics red book: annual pharmacists' reference. Oradell, N.J.: Medical Economics, 1992.
- Gordon LI, Harrington D, Andersen J, et al. Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. *N Engl J Med* 1992;327:1342-9.
- Montserrat E, Garcia-Conde J, Vinolas N, Estape J. ProMACE-cytaBOM vs. CHOP in the treatment of unfavorable lymphomas: a randomized trial. *Blood* 1991;78:Suppl 1:127a. abstract.
- Cooper IA, Ding JC, Matthews JP, et al. A randomized comparison of MACOP-B and CHOP in intermediate grade non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1991;10:271. abstract.
- Carde P, Meerwaldt JH, van Glabbeke M, et al. Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non-Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. *Ann Oncol* 1991;2:431-5.
- Federico M, Moretti G, Gobbi PG, et al. ProMACE-CytaBOM versus MACOP-B in intermediate and high grade NHL: preliminary results of a prospective randomized trial. *Leukemia* 1991;5:Suppl 1:95-101.
- Chisesi T, Santini G, Capnist G, et al. ProMACE-MOPP vs MACOP-B in high grade non-Hodgkin's lymphomas: a randomised study in a multicenter cooperative study group (NHLCSG). *Leukemia* 1991;5:Suppl 1:107-11.