American Journal of Hematology 59:156–160 (1998)

Mitoxantrone, Prednimustine, and Vincristine for Elderly Patients With Aggressive Non-Hodgkin's Lymphoma

Jonathan C. Yau,[1]* Colin Germond,[2] Stefan Gluck,[2] Christine Cripps,[1] Shailendra Verma,[1] Bruce F. Burns,[1] Terry M. Koski,[2] Diane C. Lister,[1] and Glenwood D. Goss[1]

[1]Ottawa Regional Cancer Centre, Ottawa, Ontario, Canada
[2]Northeastern Ontario Regional Cancer Centre, Sudbury, Ontario, Canada

Elderly patients with intermediate- or high-grade non-Hodgkin's lymphoma have a worse outcome than those who are younger than 60 years. It has been shown that aggressive combination chemotherapy is poorly tolerated in older patients resulting in a subsequent decrease in dose intensity. A phase II trial was conducted with mitoxantrone, prednimustine, and vincristine (NSO) in this group of patients. NSO consists of mitoxantrone 12 mg/M^2 intravenously on day one, vincristine 1.4 mg/M^2 intravenously on day 1 (maximum dose of two mg), and prednimustine 100 mg/M^2 orally once a day for four days. NSO was repeated every 21 days. Thirty-six patients were able to be evaluated. There were 18 males and 18 females with the median age of 71 (range 60–85). NSO was well tolerated and nonhematological toxicities were uncommon. More than 80% of the patients received 90% or greater of the intended dose. The complete response rate was 60.6% and partial response was 21.8%. At 60 months the Kaplan-Meier estimate of progression-free survival was 47.9% (standard error 8.6%) and actual survival was 40.6% (standard error 8.8%). There were no differences in outcome between those with performance status (PS) of zero or one and those with PS > 1. NSO is well tolerated by elderly patients including those with PS > 1. These results compare favorably with other combinations in elderly patients with aggressive non-Hodgkin's lymphoma. Am. J. Hematol. 59:156–160, 1998.

Key words: non-Hodgkin's lymphoma; elderly; mitoxantrone; prednimustine; vincristine

INTRODUCTION

Patients with intermediate- or high-grade non-Hodgkin's lymphoma are usually older than 60 years of age [1,2]. The survival rate of these patients is worse than those who are younger than 60 years of age [3–6]. The shorter survival cannot be explained by the known differences in tumor characteristics in these patient groups. It is generally believed that aggressive combination chemotherapy is poorly tolerated in older patients resulting in a subsequent decrease in dose intensity. The decrease in dose intensity may thus compromise the efficacy of combination chemotherapy. But older patients who received the full doses also had a poorer survival rate [5,6]. It is possible that older patients tend to develop more complications after therapy that resulted in early cessation of therapy after initial responses [4,7]. These observations suggest that in older patients, less toxic regiments that can be given with greater dose intensity and longer duration than those currently used might improve the complete remission rate and, consequently, long-term survival.

Prednimustine and mitoxantrone are active agents for the treatment of refractory lymphoma [8,9]. These agents are also better tolerated than other similar agents in elderly patients [10,11]. Phase II studies with regimens specifically devised for the treatment of aggressive lymphoma in older patients have been performed [7,10–14]. The outcomes of these studies are encouraging, with 30%–60% complete responses, and 20%–44% of the patients alive at three years. The toxicities tend to be higher

Contract grant sponsor: Cyanamid Lederle Canada, Inc.; Contract grant sponsor: Pharmacia Canada, Inc.

*Correspondence to: Dr. J.C. Yau, Ottawa Regional Cancer Centre, 190 Melrose Avenue, Ottawa, Ontario, Canada K1Y 4K7.

Received for publication 6 April 1998; Accepted 10 June 1998

for the more intensive combinations. These results suggest that the addition of vincristine, a nonmyelosuppressive agent, to the combination of mitoxantrone and prednimustine should be well tolerated by patients older than 60 years. This combination, when given at optimal intensity, may produce a higher remission rate and possibly improve survival.

METHODS AND MATERIALS

Written informed consent, as approved by the institutional review boards of the corresponding institutes (Laurentian Hospital, Ottawa General Hospital, and Ottawa Civic Hospital), was obtained from each patient. Patients who were at least 60 years of age with intermediate- or high-grade lymphoma, except Burkitt's or lymphoblastic lymphoma, were entered into the study. Eligibility criteria included bilirubin <50 μmol/L, Eastern Cooperative Oncology Group (ECOG) performance status of three or less, no evidence of circulating lymphoma cells in the peripheral blood by light microscopy, no evidence of central nervous system (CNS) involvement by lymphoma, no previous chemotherapy, negative human immunodeficiency virus serology. Patients with acute myocardial infarction, left ventricular ejection fraction of ⩽50%, uncontrolled hypertension, arrhythmia, or congestive heart failure, were excluded.

Pretreatment Evaluation

Before initiation of treatment, all patients had a complete history and physical examination, complete blood count, differential count, biochemistry including serum lactate dehydrogenase (LDH), bone marrow aspiration and biopsy, chest radiograph, abdominal ultrasound or computerized tomography, other radiological examination as indicated, electrocardiogram, left ventricular gated scan before or during the first course of therapy. Cerebrospinal fluid for cytology was obtained from patients with bone marrow involvement by lymphoma.

Treatment

The combination chemotherapy consisted of mitoxantrone 12 mg/M^2 intravenously on day one, vincristine 1.4 mg/M^2 intravenously on day one (maximum dose of two mg), and prednimustine 100 mg/M^2 orally once a day for four days (NSO). The chemotherapy was repeated every 21 days provided that the neutrophil count was >1.0 × 10^9/litre and the platelet count was >100 × 10^9/litre; otherwise, the therapy was delayed for one week or until recovery of the blood counts. The dosage of mitoxantrone and prednimustine was reduced by 20% for neutropenia (<0.5 × 10^9/litre) associated with fever requiring antibiotic therapy or World Health Organization (WHO) grade IV thrombocytopenia (platelet <25 × 10^9/litre). The dosage of vincristine was reduced by 50% if WHO grade II peripheral nerve toxicity or severe constipation occurred, and discontinued if grade III neurological toxicity occurred. For patients who had responses to the combination, at least six courses or two additional courses after achieving complete response were administered. No hematopoietic growth support was administered in this study.

Investigation and Assessment During Treatment

Toxicities were graded according to the WHO common toxicity criteria [15]. Weekly complete blood counts and differential counts were done. Physical examination, assessment of improvement in symptoms, serum creatinine, liver function tests, and serum LDH were done once every three weeks while the patients were on the therapy. After the fourth and sixth courses of chemotherapy, all the tests that were positive at the patient's initial evaluation were repeated.

Data Analysis and Statistical Considerations

Evaluations of clinical responses were done using standard criteria. Survival and progression-free survival curves were constructed using the method of Kaplan and Meier [16]. All analyses were performed using SPSS 7.5 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Thirty-seven patients were registered on the study between October 1989 and April 1995. One patient did not have intermediate- or high-grade lymphoma and was removed from analysis. None was found to have CNS involvement or circulating lymphoma cells. Thirty-six were evaluated for this study. One patient had diffuse small cleaved cell, two had follicular large cell, five had diffuse mixed cell, 26 had diffuse large cell, and two had immunoblastic lymphoma. There were 18 males and 18 females. The median age was 71 years (range 60–85). Eleven, 16, eight, and one had ECOG performance status (PS) of zero, one, two, and three respectively. Fourteen patients had stage II, 11 had stage III, and 11 had stage IV disease. Eight patients (22.2%) had B symptoms. Twenty (55.6%) had elevated serum LDH.

Dose Intensity

The median number of courses administered was five (range 1–13). For those who achieved a complete response, the median number of courses received was six (range 2–13). For those who received less than six courses of therapy, the treatment was discontinued because of greater than grade III toxicities. The dose intensity of the regimen received by the patients who received more than three courses of therapy are shown in Table I. More than 80% of the patients received 90% or more of the intended dose. Chemotherapy was delayed in 12 pa-

TABLE I. Estimated Doses of Mitoxantrone, Prednimustine, and Vincristine Received by 26 Patients

Estimated total dose	Mitoxantrone	Prednimustine	Vincristine
100%	15 (57.7%)	17 (65.4%)	22 (84.6%)
<100% and >89%	6 (23.1%)	4 (15.4%)	1 (3.8%)
<90% and >79%	1 (3.8%)	2 (7.7%)	2 (7.7%)
<80% and >69%	2 (7.7%)	1 (3.8%)	0
<70%	2 (7.7%)	2 (7.7%)	1 (3.8%)

tients (33.3%) during treatment. Seventeen patients (47.2%) required a dose reduction of one of the courses of chemotherapy. The median reduction in these 17 patients was 20% (range 9%–50%). There was no obvious difference in progression-free survival, cause-specific survival, and overall survival between patients who had delays or dose reduction and those who received full doses on time. However, the number of patients in this study was too few to have the statistical power to detect a difference.

Toxicities

The toxicities are shown in Table II. Nonhematological toxicities (>grade II) were uncommon. Two patients developed ileus which resolved after intravenous fluid support. One patient had bowel surgery for the diagnosis of lymphoma before chemotherapy. One patient developed severe depression after the fifth course of chemotherapy resulting in discontinuation of treatment. The majority of patients (94.4%) developed greater than grade II neutropenia. Six patients developed febrile neutropenia requiring intravenous antibiotics. One of these patients had positive blood cultures for streptococcus group B and staphylococcus aureus, and was treated successfully with antibiotics. Whereas five patients (13.9%) developed greater than grade II thrombocytopenia, only one patient required platelet transfusion support for rectal bleeding. There was no treatment-related mortality.

Responses and Survival

Two patients were not able to be evaluated for response and one patient did not have investigations to assess response. Of the remaining 33 patients, 20 (60.6%) achieved a complete response, seven a partial response, two had stable disease, and four had progression of disease. The total response rate (complete and partial responses) was 81.8%. The patient survival is shown in Figure 1. At 60 months, the Kaplan-Meier estimate of progression-free survival was 47.9% (standard error 8.6%) and actual survival was 40.6% (standard error 8.8%). Twenty patients died; fifteen died from progression of lymphoma, two from acute myocardial infarction, one from chronic obstructive lung disease, one from pulmonary embolism, and one from prostate cancer.

TABLE II. Worst Toxicity Recorded for 36 Patients on NSO Chemotherapy*

	Grade 0	Grade 1	Grade 2	Grade ⩾3
Nausea and vomiting	13	14	8	1
Mucositis	23	11	2	0
Constipation	20	12	2	2
Peripheral neuropathy	20	12	4	0
Cardiac function	34	1	0	1
Cardiac rhythm	35	1	0	0
Infection	16	8	10	2
Hemorrhage	34	1	0	1
Neutropenia	0	1	1	34
Thrombocytopenia	20	3	8	5

*NSO, mitoxantrone, prednimustine, and vincristine.

There were 27 patients with PS of zero or one and nine with PS of two or three. The progression-free survival was 46.0% (standard error 9.9%) and 56.0% (standard error 16.6%), and the overall survival was 40.0% (standard error 10.2%) and 42.0% (standard error 17.3%) for those with good PS and those with PS greater than one, respectively. There was no significant difference between the groups ($P = 0.79$, 0.81, and 0.53 respectively).

DISCUSSION

The standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administered every three weeks has been shown to be equivalent to more aggressive combinations for patients with aggressive non-Hodgkin's lymphoma [17]. The same therapy for older patients usually resulted in an inferior outcome as compared with those younger than 60 years [18,19]. The toxicity of the regimen was also worse in older patients and usually resulted in dose reductions and delays. It has also been shown that CHOP given in adequate dose intensity produces inferior results in older patients [6]. In contrast to the approach for younger patients in which new regimens tend to be more dose intensive and toxic than standard CHOP, regimens designed for older patients tend to consist of agents with less toxicities. Phase II trials of these combinations showed promising outcomes with three-year overall survival ranging from 21%–44% [7,10–14].

Prednimustine is 21-prednisolone ester of chlorambucil [20]. After oral administration, it is rapidly hydrolyzed to chlorambucil and prednisolone. However, prednimustine's improved therapeutic action and its pharmacokinetic profile separates it from chlorambucil. In phase II studies it has been shown to be well tolerated and has activity in relapsed and refractory aggressive non-Hodgkin's lymphoma [8]. Mitoxantrone is an anthracenedione which causes less nausea, vomiting, mucositis, and cardiotoxicity than does doxorubicin. It has demonstrated efficacy in non-Hodgkin's lymphoma and may be

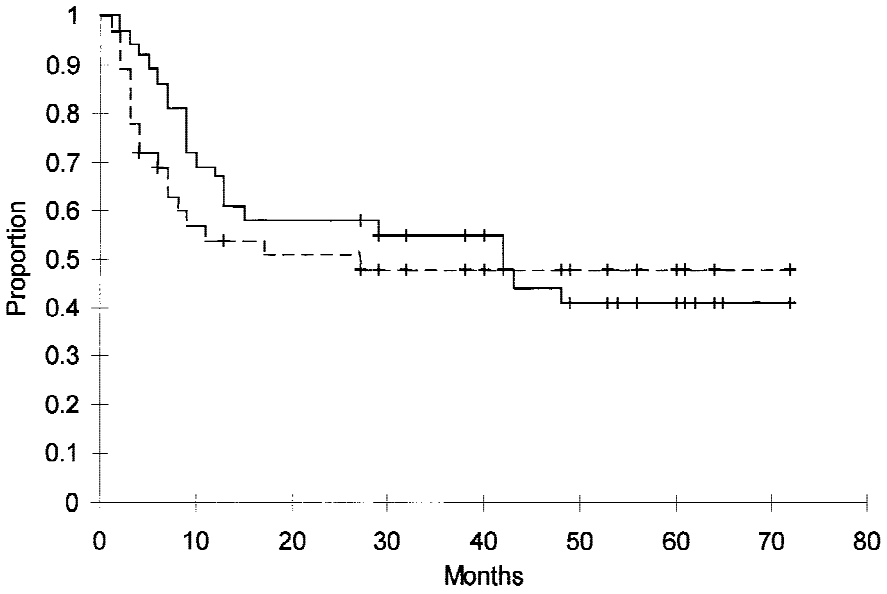

Fig. 1. Survival of patients treated with NSO with progression-free survival (broken line) and overall survival (solid line).

better tolerated in older patients [9]. Maintaining adequate functional status without compromising the outcome is important in elderly patients. Combination of these less toxic agents may therefore be better tolerated and thus allow full doses to be administered for the initial course and the dose intensity maintained for the subsequent courses in older patients.

In our study, the combination was well tolerated and nonhematological toxicities were uncommon. There was no treatment-related morality. More than 80% of the patients received 90% or greater of the intended dose. In this small study we were unable to detect any relationship between the dose intensity and progression-free survival, or overall survival.

Recently, the results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group that compared etoposide, mitoxantrone, and prednimustine (VMP), vs. CHOP in patients older than 70 years of age with intermediate- and high-grade non-Hodgkin's lymphoma was reported [21]. Neurologic and gastrointestinal toxicities were significantly more common with CHOP. Overall, objective response rates were significantly better in CHOP-treated patients. At two years, the progression-free and overall survival rate was 25% and 30% compared with 55% and 65% for VMP and CHOP respectively. In this study, the dosages of chemotherapy were started at 75% of optimal dosage if PS of patients were greater than one. Whereas this reduction may be appropriate for CHOP, which causes more toxicities, it may not be necessary for less toxic regimens designed for older patients. The response rate and survival of patients receiving CHOP were similar to NSO. In our study, there was no initial dose reduction according to the PS of patients. Although the toxicities of CHOP may not allow it to be administered at full doses for those with poor PS, NSO appears to be well tolerated even at full doses in this group of patients. With NSO, the outcome of those with PS zero or one and those greater than one was not significantly different. Whereas it is unlikely that NSO will improve the outcome of elderly patients with good PS when compared with CHOP, it may be better tolerated by those with poor PS and result in better outcomes. Further studies may be needed to define the optimal therapy for this subset of patients.

The combination of mitoxantrone, prednimustine, and vincristine has activities similar to other regimens, including CHOP, in elderly patients with aggressive non-Hodgkin's lymphoma. This combination is well tolerated by elderly patients including those with PS greater than one. NSO may be a more appropriate combination for those with poor performance status who would otherwise receive reduced doses of CHOP.

REFERENCES

1. Devesa SS, Fears T: Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 52(suppl 19):5432s–5440s, 1992.
2. Ries LAG, Hankey BF, Miller BA, Hartman AM, Edwards BK: Cancer Statistics Review 1973–1988. Bethesda, MD: National Cancer Institute; NIH publication 91-2789:II.34-II.35, 1991.
3. Shipp MA, Harrington DP, Anderson JR, et al.: A predictive model for aggressive NHL: The international non-Hodgkin's lymphoma prognostic factors project. N Engl J Med 329:987–994, 1993.
4. Vose JM, Armitage JO, Weisenburger DD, Bierman PJ, Sorensen S, Hutchins M, Moravec DF, Howe D, Dowling MD, Mailliard J, Johnson PS, Pevnick W, Packard WM, Okerbloom J, Thompson RF, Langdon RM, Jr, Soori G, Peterson C: The importance of age in survival of patients treated with chemotherapy for aggressive non-Hodgkin's lymphoma. J Clin Oncol 6:1838–1844, 1988.
5. Orlandi E, Lazzarino M, Brusamolino E, Castelli G, Pagnucco G,

Morra E, Bernasconi C: Non-Hodgkin's lymphoma in the elderly: The impact of advance age on therapeutic options and clinical results. Haematologica 76:204–208, 1991.
6. Dixon DO, Neilan B, Jones SE, Lipschitz DA, Miller TP, Grozea PN, Wilson HE: Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma: The SWOG experience. J Clin Oncol 4:295–305, 1986.
7. Tirelli U, Zagonel V, Serraino D, Thomas J, Hoerni B, Tangury A, Ruhl U, Bey P, Tubiana N, Breed WPM, Roozendaal KJ, Hagenbeek A, Hupperets PS, Somers R: Non-Hodgkin's lymphoma in 137 patients aged 70 years or older: A retrospective EORTC lymphoma group study. J Clin Oncol 6:1708–1713, 1988.
8. Pedersen-Bjergaard J, Mork-Hansen M, Geisler CH, Nissen NI: Clinical trial of prednimustine, Leo 1031 in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia previously treated with steroids and alkylating agents. Acta Med Scand 207:215–220, 1980.
9. Coltman CA, Jr, Coltman TM, Balcerzak SP, Morrison FS, Von Hoff DD: Mitoxantrone in refractory non-Hodgkin's lymphoma, a SWOG study. Semin Oncol 11:50–53, 1984.
10. Tirelli U, Carbone A, Zagonel V, Veronesi A, Canetta R: Non-Hodgkin's lymphomas in the elderly: Prospective studies with specifically devised chemotherapy regimens in 66 patients. Eur J Cancer Clin Oncol 23:535–540, 1987.
11. Zagonel V, Tirelli U, Carbone A, Errante D, Morassot S, Sorio R, Monfardini S: Combination chemotherapy specifically devised for elderly patients with unfavorable non-Hodgkin's lymphoma. Cancer Invest 8:575–580, 1990.
12. Tirelli U, Zagonel V, Errante D, Serraino D, Talamini R, De Cicco M, Carbone A, Monfardini S: A prospective study of a new combination chemotherapy regimen in patients older than 70 years with unfavorable non-Hodgkin's lymphoma. J Clin Oncol 10:228–236, 1992.
13. O'Reilly SE, Klimo P, Connors JM: Low-dose ACOP-B and VABE: Weekly chemotherapy for elderly patients with advanced-stage diffuse large cell lymphoma. J Clin Oncol 9:741–747, 1991.
14. O'Reilly SE, Connors JM, Howdle S, Hoskins P, Klasa R, Klimo P, Stuart DS: In search of an optimal regimen for elderly patients with advanced stage diffuse large cell lymphoma: Results of a phase II study of P/DOCE chemotherapy. J Clin Oncol 11:2250–2257, 1993.
15. Miller AB, Hoogstraten B, Staquet M, Winckler A: Reporting results of cancer treatment. Cancer 47:207–214, 1981.
16. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
17. Fisher RL, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA, Jr, Miller TP: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002–1006, 1993.
18. Armitage JO, Potter JF: Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly. Increased complications of advancing age. J Am Geriatr Soc 32:269–273, 1984.
19. Miller TP, Jones SE: Initial chemotherapy for clinically localized lymphomas of unfavorable histology. Blood 62:413–418, 1983.
20. Bastholt L, Johansson CJ, Pfeiffer P, Svensson L, Johansson SA, Gunnarsson PO, Mouridsen H: A pharmacokinetic study of prednimustine as compared with prednisone plus chlorambucil in cancer patients. Cancer Chemother Pharmacol 28:205–210, 1991.
21. Tirelli U, Errante D, Van Glabbeke M, Teodorovic I, Kluin-Nelemans JC, Thomas J, Bron D, Rosti G, Somers R, Zagonel V, and Noordijk EM: CHOP is the standard regimen in patients greater-than or equal to 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: Results of a randomized study of the EORTC lymphoma cooperative study group. J Clin Oncol 16:27–34, 1998.