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Non-Hodgkin's Lymphoma in Elderly Patients: a Phase II Study of MCOP Chemotherapy in Patients Aged 70 Years or Over With Intermediate- or High-grade Histology

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During the period 1 January 1988 to 31 July 1991, 74 patients were seen with intermediate- or high-grade non-Hodgkin's lymphoma who were aged 70 years or over. Of these 74 patients, 20 were treated with radiotherapy alone, and 46 were judged as suitable for treatment with the chemotherapy regime MCOP (mitoxantrone, cyclophosphamide, vincristine and prednisolone). Involved field radiotherapy (35–40 Gy in 20 fractions over 4 weeks) was given to 14 of the 21 patients with stage IA and IIA disease, and 6 of the 25 patients with stage III and IV disease after completion of chemotherapy. The complete response rate was 63% at the completion of all treatment (6 months), and 39% at 12 months. There were no treatment-related deaths, and the 3-year cause-specific survival was 26% (overall survival 21%). For patients aged 70–75 years, the 3-year cause-specific survival was 34% in comparison to 17% for those patients aged 76-93 years. The chemotherapy was well tolerated by those patients aged 70 years and over, 70% of the patients did not vomit and no patients had significant vincristine neuropathy. There were only four infections associated with neutropenia. All patients completing six cycles had moderate, patchy alopecia. This MCOP regime is suitable for patients aged 70 years and over with intermediate- and high-grade non-Hodgkin's lymphoma. The survival of patients is comparable to that obtained with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) with less apparent toxicity.

Key words: non-Hodgkin's lymphoma, elderly patients, chemotherapy
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INTRODUCTION

PATIENTS AGED 70 years or older with intermediate- or high-grade non-Hodgkin's lymphoma are often not entered in clinical trials. If they are, they tend to be the fitter patients who could tolerate the chemotherapy regimes of the trial without dose reduction. If the survival of these patients is analysed, it is likely to be better than that for unselected patients of similar age. If lymphoma groups adopt a uniform policy for treating patients aged 70 years or older, it will be possible to find out the survival of all the patients in this age group. Even then, some patients will not be suitable for any form of active treatment, and some patients are only diagnosed at autopsy.

In the Nottinghamshire Lymphoma Group, we decided to treat all patients aged 70 year or older with intermediate- or high-grade non-Hodgkin's lymphoma with MCOP (mitoxantrone, cyclophosphamide, vincristine and prednisolone) if these patients were not suitable for treatment by radiotherapy alone (non-bulky stage IA).

PATIENTS AND METHODS

During 1986–1987, a pilot study of MCOP chemotherapy was carried out on 11 patients (8 males, 3 females) with an age range of 68 to 82 years (median age 77), who were suffering from previously untreated intermediate- and high-grade non-Hodgkin's lymphoma. These patients were considered medically unfit for doxorubicin-containing chemotherapy regimes, mainly because of ischaemic heart disease. 10 patients had a B-cell centroblastic and one peripheral T-cell (mixed small and large cell) non-Hodgkin's lymphoma. The stages at presentation were IIA 4, IVA 1 and IVB 6. 2 of the patients with IIA disease had tonsillar lymphoma. The intended regime was mitoxantrone 6–10 mg/m^2, cyclophosphamide 500–600 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg) all given intravenously on day 1, with prednisolone 20 mg, twice a day, orally for 5 days. The cycles were given every 21 days. The lower dose was used for

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the first cycle, and the dose was increased (if possible) with subsequent cycles depending on toxicity.

A decision was made in 1987 based on the results of this pilot study to treat all patients (≥ 70 years) with newly diagnosed intermediate- and high-grade non-Hodgkin's lymphoma with MCOP (bulky stage IA and stages IIA-IVB).

The three clinicians treat all the patients with intermediate- and high-grade non-Hodgkin's lymphoma presenting in Nottingham and Central Nottinghamshire Health Authorities (combined served population 915 000).

The study was started on 1 January 1988. The regime was mitoxantrone 10 mg/m^2, cyclophosphamide 600 mg/m^2, vincristine 1 mg (only), all given intravenously on day 1, with prednisolone 20 mg, twice a day, orally for 5 days. The intention was to give six cycles at an interval of 21 days. It was also planned for patients with stage I and II disease to receive involved field radiotherapy (35–40 Gy in 20 fractions over 4 weeks) 4–6 weeks after completion of chemotherapy (excluding gastrointestinal tract).

From 1 January 1988 to 31 July 1991, there were 222 patients (aged > 15 years) with intermediate- and high-grade non-Hodgkin's lymphoma recorded on the registers of the three hospitals with departments of histopathology in the two Health Authorities. 77 (35%) were aged 70 years or more. The histological material on all 77 patients was reviewed and 74 patients were confirmed as having intermediate- or high-grade non-Hodgkin's lymphoma. The histology in 1 patient was mixed cellularity Hodgkin's disease, in 1 patient follicular centrocytic centroblastic non-Hodgkin's lymphoma and in 1 patient the material was insufficient for classification. Of these 74 patients, 46 were entered into the MCOP study. 20 patients were treated with radiotherapy alone, 14 with stage IA disease were treated radically, 3 with stage IIA and 3 with stage IVA were treated palliatively. 6 patients, who were terminally ill at presentation, were considered unfit for any type of active treatment.

One patient had primary central nervous system lymphoma and was treated with the BVAM (BCNU, vincristine, cytosine arabinoside and methotrexate)/radiotherapy protocol [1]. One patient received CHOP chemotherapy. The median age of the 46 patients was 75 years (range 70–93); the male to female ratio was 23:23; 32 (70%) had symptoms A and 14 (30%) had symptoms B. The stages at presentation were IA 2, IIA 17, IIB 2, IIIA 11, IIIB 4, IVA 2 and IVB 8.

The staging investigations included computed tomography (CT) scanning of chest, abdomen and pelvis, and bone marrow aspirate and trephine, in addition to a full blood count, and measurement of urea and electrolytes, calcium, lactate dehydrogenase, and liver function tests and immunoelectrophoresis. Patients aged > 80 years, who did not wish to have CT scanning, had an abdominal ultrasound and a chest radiograph. Bone marrow examination was omitted in these cases. The review of the histology for the 46 patients treated with MCOP is given in Table 1. The majority of patients (74%) had B-cell diffuse centroblastic non-Hodgkin's lymphoma. Of the 21 patients with stage I and II disease, 18 (86%) had an extranodal presentation (tonsil 7, thyroid 3, maxillary antrum 3, posterior tongue 1, nasopharynx 1, stomach 1, testicle 1, skin 1). Only 5 (20%) of the 25 patients with stage III or IV disease had predominantly extranodal presentation (small bowel 3, tonsil 1, maxillary antrum 1). For patients aged 70–75 years, the stages were I 1, II 9, III 6, IV 8. For those aged 76–93 years, the stages were I 1, II 10, III 9, IV 2. There was no significant difference in histological type or other staging investigations between these two age groups.

Table 1. Histological subtypes of intermediate- and high-grade non-Hodgkin's lymphoma in 46 patients aged 70 years and over

Histological subtype	No. of patients
B-cell diffuse centroblastic	34
B-cell immunoblastic	3
T-cell pleomorphic medium and large cell	3
High-grade unclassifiable	6

RESULTS

Pilot MCOP study

The mean number of cycles given was four. The mean total mitoxantrone dose per patient was 30 mg/m^2 and for cyclophosphamide was 2300 mg/m^2. Vincristine and prednisolone were given as planned. 2 patients with stage IIA disease were also given involved field radiotherapy (35–40 Gy in 20 fractions over 4 weeks) 4–6 weeks after completing chemotherapy. The chemotherapy was well tolerated, and no patients refused to continue treatment. All patients completing six cycles had WHO grade 2 alopecia (moderate patchy). Nausea was mild (grade 0/1). 3 patients had grade 3 neutropenia (0.5–0.9 × 10^{9}1) and 1 patient had grade 2 neutropenia. No patient required a blood transfusion because of chemotherapy, and there was no significant thrombocytopenia. There was one episode of neutropenia-associated septicaemia, but no treatment-related deaths. The complete response rate at 6 months was 54%, and the 3-year survival was 18%. All of the 11 patients have now died; no patient survived 5 years.

Phase II MCOP study

Treatment given. The mean number of cycles given was 4.8. 7 patients received only one cycle bcause of progressive disease. 29 patients (63%) received six cycles. No patient received more than six cycles. Dose reduction and treatment delay only occurred because of neutropenia. Only the dose of mitoxantrone was reduced in 10 (4.5%) of 222 cycles (8 mg/m^2 8, 6 mg/m^2 1, omitted 1). Treatment was delayed on only 14 cycles (6%). Involved field radiotherapy (35–40 Gy in 20 fractions over 4 weeks) was also given to 14 of the 21 patients with stage I or II disease 4–6 weeks after completing radiotherapy. In the 7 patients who did not receive involved field radiotherapy, the reasons were fractured femur 1, patient refusal 4, progressive disease 1, gastric presentation 1. Involved field radiotherapy (35–40 Gy in 20 fractions over 4 weeks) was given to 6 patients with stage III or IV disease because of partial response at the site of bulk disease.

Toxicity. This is described in Table 2, and toxicity was generally mild. Only 10 patients required antibiotics for infection, and only 4 of these were associated with neutropenia (< 1.5 × 10^9/l). In the six infections not associated with neutropenia, three were chest infections in patients with chronic obstructive airways disease, one was a wound infection (from initial biopsy), one was oropharyngeal candidiasis and one was undetermined. 2 other patients had significant morbidity/toxicity: perforated duodenal ulcer and myocardial infarcation.

Table 2. Toxicity of the MCOP regime

	WHO grade				
	0	1	2	3	4
Anaemia	23	18	4	1	0
Neutropenia	29	7	6	1	3
Thrombocytopenia	45	1	0	0	0
Nausea/vomiting*	25	7	11	3	0
Alopecia† (> 1 cycle)	0	6	29	4	0

Values are the number of patients with each grade of toxicity. The grade is the worst observed during the course of chemotherapy. The nadir neutrophil count was not determined, and the severity of neutropenia may have been under-estimated. * No patient received 5-HT_3 antagonists. † All female patients chose to wear a wig.

Response and survival

The complete response rate was 63% at the completion of all treatment (6 months from the start of treatment), and 39% at 1 year (Figure 1). The high response rate of 63% at 6 months was due both to the high percentage of patients with localised disease (46% stage I or II), and the additional involved field radiotherapy. There were no treatment-related deaths, and the 3-year cause-specific survival was 26% (overall survival 21%) (Figure 1). Age was not a prognostic factor for survival, although the overall survival at 3 years was 27% for patients aged 70–75 years, as against 16% for those aged 76–93 years (Figure 2). The complete response rate was 74% for patients aged 70–75 years, and 50% for those aged 76–93 years (6 months from the start of treatment; Figure 3).

The overall disease-free and cause-specific survival is given in Table 3 for the 46 patients treated with MCOP chemotherapy, and for the 24 patients aged 70–75 years, and for the 22 patients aged 76–93 years. The cause-specific survival at 3 years was 34% for patients aged 70–75 years, and 17% for those aged 76–93 years (Figure 4).

The overall survival of these patients was corrected using data on the expected survival of a normal population aged 70–75 and 76–96 years, respectively [2]. The corrected survival curve matches the cause-specific survival curve for each age group (Figure 4). 31 patients have died from non-Hodgkin's lymphoma at the time of analysis (1 November 1992).

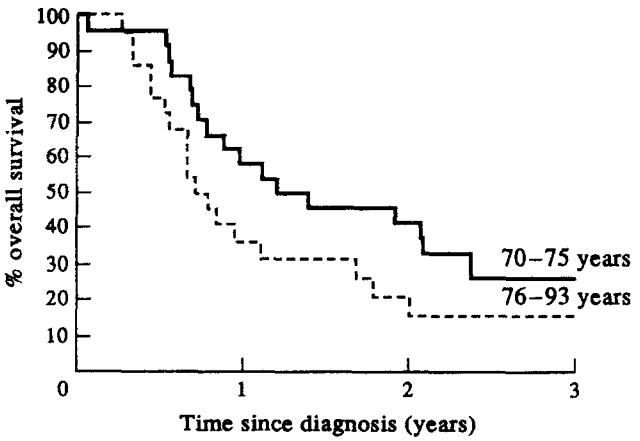

Figure 2. The actuarial overall survival of 24 patients (aged 70–75 years) treated with MCOP (————) and the actuarial overall survival of 22 patients (aged 76–93 years) treated with MCOP (----).

4 patients died from illnesses unrelated to non-Hodgkin's lymphoma. The patient with a perforated sigmoid diverticulum died 5 days after starting MCOP chemotherapy. The patient with the fractured neck of femur died of pneumonia 4 months after completing chemotherapy. The third patient died of aortic valve stenosis 15 months after completing chemotherapy. He was considered unfit for aortic valve replacement. A fourth patient died of a myocardial infarcation 25 months after completing chemotherapy. He had a history of ischaemic heart disease at diagnosis. None of the last 3 patients had evidence of recurrence of lymphoma on clinical assessment at their last clinic appointment.

DISCUSSION

The age distribution of 222 adult patients with intermediate and high-grade non-Hodgkin's lymphoma has been determined from the pathology registers of the Nottinghamshire hospitals. One third of patients were aged 70 year and over, one third were aged 55–69 years, and one third were aged 15–54 years. D'Amore and colleagues [3] similarly found that 40% of patients with intermediate- and high-grade non-Hodgkin's lymphoma were aged 70 years and over. Almost all the patients with intermediate- and high-grade non-Hodgkin's lymphoma aged 70 years and

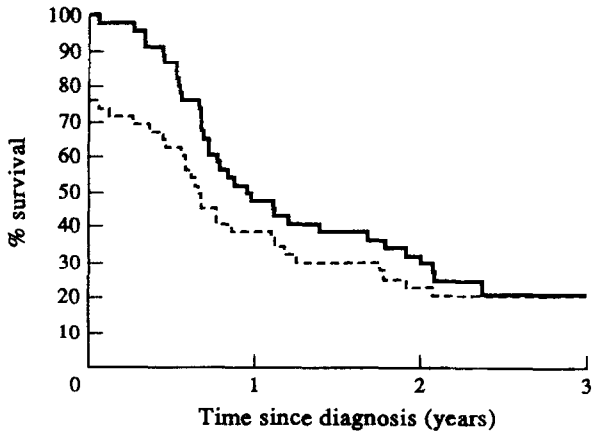

Figure 1. The actuarial overall survival of 46 patients (aged 70–93 years) treated with MCOP (————) and the actuarial disease-free survival (----).

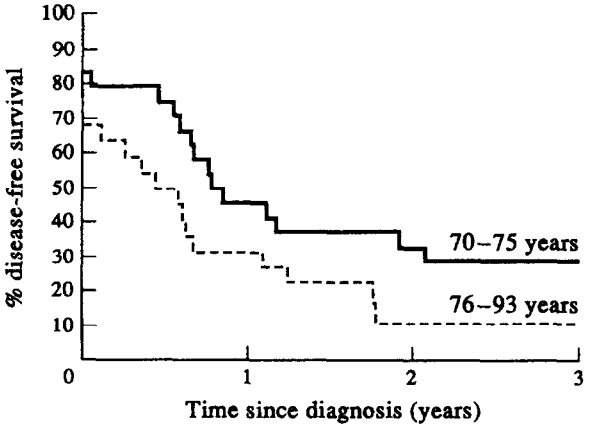

Figure 3. The actuarial disease-free survival of 24 patients (aged 70–75 years) treated with MCOP (————) and the actuarial disease-free survival of 22 patients (aged 76–93 years) treated with MCOP (----).

Table 3. Three-year survival of patients with intermediate- and high-grade non-Hodgkin's lymphoma aged 70 years and over treated with MCOP

Age (years)	No. of patients	Overall (95% CI)	Disease-free (95% CI)	Cause-specific (95% CI)
70–93	46	21 (9–33)	21 (9–33)	26 (14–38)
70–75	24	27 (9–45)	29 (11–47)	34 (13–55)
76–93	22	16 (2–30)	11 (0–25)	17 (0–34)

CI, confidence interval.

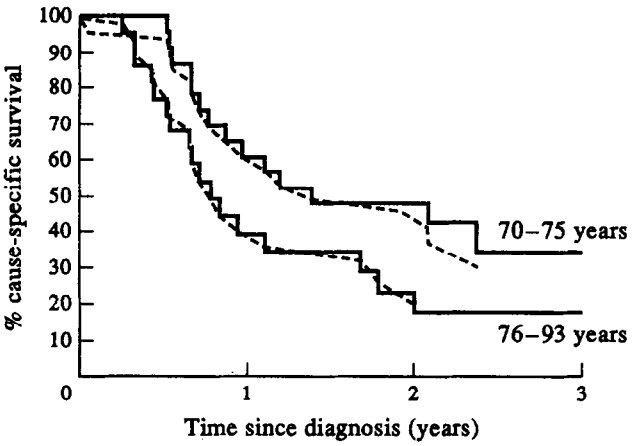

Figure 4. The actuarial cause-specific survival of 24 patients (aged 70–75 years) and 22 patients (aged 76–93 years) treated with MCOP (————). The actuarial overall survival curve corrected for the deaths from other causes which would be expected from survival data on an age-matched normal population (----). The difference in survival between those patients aged 70–75 years and those aged 76–93 years is non-significant by logrank analysis ($\chi^2 = 3.44$, $P = 0.07$).

over, who were considered suitable for treatment with chemotherapy, were treated with the MCOP regime.

Of the 74 patients aged 70 years and over presenting over a 3.5-year period, 14 (19%) were stage IA and suitable for treatment by radiotherapy alone, 60 (81%) were stages IA bulky - IVB. Of these 60 patients, 46 (77%) were treated with MCOP and 12 patients were considered unfit for any chemotherapy (5 of these patients received radiotherapy). Our patients underwent considerably less selection than is the case when patients are entered into phase II and III trials with no specified upper age limit. Often only fit elderly patients are entered into such trials. For this reason, the survival of patients over 70 years may appear to be a good deal more optimistic than it really is.

Thus, in the present study of relatively unselected patients (aged 70–93 years), the cause-specific survival at 3 years was 26%; for patients aged 76–93 years the cause-specific survival was only 17% in comparison to 34% for those aged 70–75 years. Although this survival difference was non-significant, intermediate- and high-grade non-Hodgkin's lymphomas do appear to be more aggressive in the very elderly. D'Amore and colleagues [3] found that the 7-year survival for patients in West Denmark aged 70 years and over with low-, intermediate- and high-grade non-Hodgkin's lymphoma was 48, 38 and 22%, respectively. The 3-year survival for those patients with diffuse B-cell centroblastic histology was 38% (all stages).

The MCOP regime appears to produce similar survival to CHOP in patients aged 70 years and over [4] with less toxicity (Table 4). The MCOP regime was used in this phase II study both because the toxicity in elderly patients was found to be acceptable in the pilot study, and the substitution of mitoxantrone for doxorubicin has, so far, not been shown to reduce either the response rate or the survival in patients with intermediate- and high-grade non-Hodgkin's lymphoma [5–7].

In recent years, there have been a few studies in which a chemotherapy regime has been used which is suitable for the

Table 4. Review of published studies of chemotherapy in elderly patients with previously untreated intermediate- and high-grade non-Hodgkin's lymphoma

Authors		Chemotherapy regimen	No. of patients	Age range (years)	Complete response (%)	Survival
Armitage and Potter [4]	(1984)	CHOP	20	70–94	45	35 (3 years)
Vose *et al.* [11]	(1988)	CAP/BOP	112	60–91	61	34 (5 years)
Sonneveld and Michiels [8]	(1990)	MCOP	28	57–86	57	60 (2 years)
Zagonel *et al.* [12]	(1990)*	VP	35	71–88	46	31 (4 years)
McMaster *et al.* [13]	(1991)	BECALM	26	65–84	42	38 (4 years)
O'Reilly *et al.* [14]	(1991)	ACOP-B	40	66–85	65	27 (6 years)
O'Reilly *et al.* [14]	(1991)	VABE	32	64–84	63	36 (4 years)
Tirelli *et al.* [12, 15]	(1992)	VMP	38	71–92	50	19 (4 years)
Bessell *et al.*	(1994)	MCOP	46	70–93	63	21 (3 years)

* Includes 13 previously treated patients. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), CAP/BOP (cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine and prednisone), MCOP (mitoxantrone, cyclophosphamide, vincristine and prednisolone), VP (etoposide and prednimustine), BECALM (bleomycin, etoposide, cyclophosphamide, doxorubicin, methotrexate and prednisone), ACOP-B (doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone), VABE (etoposide, doxorubicin, bleomycin and prednisone), VMP (etoposide, mitoxantrone and prednimustine).

majority of patients aged over 70 years (Table 4). The complete response rate of 63% obtained in our MCOP study at 6 months from the start of treatment compares favourably with these studies.

In addition, only 21% of patients had grade 2 or more neutropenia, and there were no treatment-related deaths (Table 2). The lower incidence of neutropenia, in contrast to the study of Sonneveld and Michiels [8] resulted from the lower dose of cyclophosphamide (600 mg/m^2 instead of 750 mg/m^2), and from the fact that nadir counts at 10–14 days were not measured routinely in our study.

The toxicity of the MCOP regime was acceptable to elderly patients, with 63% of patients receiving all six cycles with little dose reduction or treatment delay. There was no nausea or vomiting in 25 patients (54%), and no vomiting in 32 patients (70%) without the use of $5HT_3$ antagonists. There was no peripheral neuropathy with the lower dose of vincristine, and the alopecia after six cycles was moderate and patchy, so that adequate re-growth of hair was accomplished reasonably quickly. Rather than attempting escalation of dose in elderly patients, some dose reduction may be valuable to reduce toxicity without compromising survival significantly.

This is supported by Tirelli and colleagues [9] who analysed, retrospectively, 137 patients aged 70 years or older seen in 13 European institutes in 1984. These patients represented 28% of all patients with non-Hodgkin's lymphoma; a similar percentage to that in Nottinghamshire. Seventy-three per cent of patients had intermediate- or high-grade histology, and 60% were stage I and II (53% in Nottinghamshire).

Similar complete response rates were obtained for intermediate- and high-grade non-Hodgkin's lymphoma with "aggressive" and "conservative" treatments (for stages II, III and IV, 31% CR with "aggressive" treatment, and 33% with "conservative" treatment). The toxicity was significantly greater, [10] with "aggressive" treatments (22.5% had grade 3 or 4 toxicity, including 11.3% of treatment-related deaths, in comparison to 5.8% grade 3 or 4 toxicity with the "conservative" treatments and 0% treatment-related deaths). The overall median survival for all 137 patients was 37 months.

In contrast, Vose and colleagues [11] have reported data from their CAP/BOP study (Table 4) in which the difference in 5-year survival (62% for those aged < 60 years as compared with 34% for those aged > 60 years) was attributed to death from unrelated causes. However, when death are attributed to other causes, the cause-specific survival (including treatment-related deaths) can be checked against the corrected overall survival using data on the expected survival of a normal population with the same age distribution. In the present study, the corrected overall survival matches the cause-specific survival, confirming that the number of deaths attributed to other causes was as expected (Figure 4).

In summary, the MCOP regime can be used in the majority of patients aged 70 years or older with intermediate- and high-grade non-Hodgkin's lymphoma. Dose reduction during the course of chemotherapy is usually not necessary.

The toxicity is acceptable, with no treatment-related deaths. The cause-specific survival for patients aged 70–75 years of 34% at 3 years is similar to that obtained with CHOP. For patients aged over 75 years, chemotherapy with MCOP is largely palliative with a cause-specific 3-year survival of 17%. A randomised phase III study of MCOP versus CHOP (doxorubicin 30 mg/m^2) in patients aged 70 years and over with intermediate- and high-grade non-Hodgkin's lymphoma by the Central Lymphoma Group (U.K.) is in progress.

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