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# A new approach to the treatment of advanced high-grade non-Hodgkin's lymphoma – intensive two-phase chemotherapy

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**Summary.** A total of 110 patients with high-grade non-Hodgkin's lymphoma (NHL) not previously treated by chemotherapy or by radiotherapy at more than one site of disease underwent a regimen comprising an intensive 6-week initial, induction phase using vincristine, adriamycin, methotrexate, and prednisolone (VAMP) followed by the non-cross-resistant combination cyclophosphamide, etoposide, and vindesine (EEE). The median age of patients was 54 years, the majority having stage IV disease. The median follow-up was 34 months and all patients have completed treatment. The overall complete remission (CR) rate for all patients was 68%. The initial phase of treatment produced a CR rate of 49%. The full regimen was completed by 87 patients, and of these, 66 (76%) achieved CR. Of those achieving CR, 72% were relapse-free, on an actuarial basis, at 2 years. Overall 2-year survival was 53%, with a median survival of 31 months. The survival of older patients and those with lymphoblastic histology was comparable to that of other groups. The survival prospects of patients with stage IV disease was not as good as that of other patients, with a significant trend to shorter survival in patients with more advanced disease. Toxicity was predictable and manageable for both phases of the regimen, although it was more severe for the initial phase. Dose-limiting toxicities were neutropenia and mucositis. This regimen is active in the treatment of advanced high-grade NHL with acceptable toxicity. These results have encouraged us to continue the study of weekly chemotherapy, which we will compare with standard cyclical chemotherapy in a prospective, randomized trial.

## Introduction

The majority of patients with high-grade non-Hodgkin's lymphoma (NHL) present with disseminated disease incurable by local modalities of treatment. Only those patients who achieve a complete remission (CR) following treatment have any chance of long-term survival, and attempts to improve the outlook depend on improving the CR rate produced by combination chemotherapy.

The theoretical work of Goldie and Coldman [11] has suggested that early exposure to multiple non-cross-resistant drugs will increase cell kill and the chance of achieving CR. Earlier work by one of us has shown that, if chemotherapy is given weekly to prevent tumor regrowth between courses, high CR rates can be achieved in a short period [3]. Methotrexate (MTX) is an active drug in high-grade NHL and has a spectrum of side effects different from that of most chemotherapeutic agents. It can be added to standard chemotherapy regimens with little increase in overall toxicity and with possible increased efficacy [6, 8, 12]. In an attempt to increase the CR rate and overall survival produced by VAP [vincristine (V), adriamycin (A), prednisolone (P)] as previously described by Blackledge et al. [3], we added MTX to this combination and followed this initial, intensive, 6-week induction regimen (VAMP) with the non-cross-resistant combination etoposide (VP-16, Vepesid), cyclophosphamide (Endoxana), and vindesine (Eldesine) given on a standard 3-week cycle (EEE). Depending on the remission status of patients prior to starting EEE, this phase of treatment represented either alternative remission induction or consolidation therapy.

## Materials and methods

*Study group.* A total of 110 patients with a histopathological diagnosis of high-grade NHL who had not previously received chemotherapy or radiotherapy at more than one site of disease were treated with this regimen. The study group comprised a consecutive series of patients being treated for advanced high-grade NHL with curative intent. Patients excluded were those in whom intensive chemotherapy with curative intent was clearly inappropriate or poor renal function made treatment with high-dose methotrexate inadvisable. Patients with previous other malignancies were also excluded, as were patients aged 80 or over. Characteristics of the study group are summarized in

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**Table 1.** Characteristics of patients at entry to study

| | | | n | % |
|---|---|---|---|---|
| Age distribution | | age < 50 | 45 | (41) |
| Age range | 15–78 | age 50–59 | 24 | (22) |
| Median age | 54 | age 60–69 | 30 | (27) |
| | | age 70+ | 11 | (10) |
| Sex | | | | |
| Female | 40 | | | |
| Male | 70 | | | |

| | n | % | | n | % |
|---|---|---|---|---|---|
| Stage[7] | | | | | |
| B symptoms | 68 | (62) | stage I | 8 | (7) |
| No B symptoms | 42 | (38) | stage II | 24 | (22) |
| | | | stage III | 20 | (18) |
| | | | stage IV | 58 | (53) |

| Sites of stage IV disease (all sites) | | | |
|---|---|---|---|
| In addition to nodal disease, | | With no nodal involvement, | |
| Liver | 15 | GI | 1 |
| Gastrointestinal (GI) | 14 | Bone | 1 |
| Lung | 11 | Liver | 1 |
| Bone marrow | 10 | | |
| Skin | 9 | | |
| Bone | 3 | | |
| Other | 2 | | |

| | | |
|---|---|---|
| Previous radiotherapy | 9 | (8) |
| Maximum bulk of disease | | |
| Not measurable | 13 | (12) |
| < 5 cm | 30 | (27) |
| 5–10 cm | 33 | (30) |
| > 10 cm | 34 | (31) |
| Histological type | | |
| Centroblastic/immunoblastic | 49 | (45) |
| Lymphoblastic | 13 | (12) |
| High-grade NOS (reviewed) | 40 | (36) |
| High-grade NOS (not reviewed) | 8 | (7) |

Table 1. Staging laparotomies were not routinely carried out, intraabdominal disease normally being assessed by CT scan. All eight stage I patients had bulky disease (> 10 cm max. diameter) or incompletely resected gastrointestinal (GT) disease, for which radiotherapy was not considered appropriate first-line treatment.

Histopathological material from 102 patients was reviewed by a panel of five histopathologists with a special interest in lymphoma. The panel viewed histopathological material, initially alone and later together, and agreed on a diagnosis for each patient. Classification was based on the Keil classification, with the following grouping adopted for the purposes of this study: (A) HGL-lymphoblastic (working formulation = lymphoblastic and small, non-cleaved cell); (B) HGL-centroblastic or immunoblastic (working formulation = diffuse, large cell and large cell, immunoblastic); (C) HGL-large cell, not otherwise classifiable (working formulation = intermediate or high-grade type but not further classifiable); (D) non-high-grade lymphoma. Histopathological material from the remaining eight patients was seen by only one member of the panel and was allocated to either group C or D.

*Treatment.* Scheduling and doses for the initial (VAMP) and consolidation phases of treatment (EEE) are shown in Fig. 1. EEE was given to CR plus three cycles with a maximum of eight cycles; patients in CR at the end of VAMP received only three cycles of EEE. If the neutrophil count was below $1.0 \times 10^9$/l or the platelet count below $50 \times 10^9$/l, treatment with VAMP or EEE was delayed by 1 week. If the neutrophil count was between 1.0 and $2.5 \times 10^9$/l or the platelet count between 50 and $100 \times 10^9$/l, then myelosuppressive drugs (adriamycin in VAMP, all drugs in EEE) were given at 50% of the protocol dose. In other cases, full doses were given except where severe toxicity had occurred or when the general condition or age of the patients was felt to warrant dose modification. The majority of patients received treatment on an outpatient or day-case basis. Patients with lymphoblastic lymphoma did not routinely receive intrathecal methotrexate or cranial prophylaxis.

*Assessment of response and toxicity.* The standard criteria for response and toxicity of the World Health Organization (WHO) as previously defined by Miller et al [19] were used for all patients. In particular, CR required the disappearance of all clinical disease, with all abnormal investigations returning to normal for a minimum of 2 months.

*Statistical methods.* Data for patients in the study were stored on a VAX 8730 minicomputer and analyzed using the BMDP statistical software package [9]. The incidence of toxicity in different groups was compared using the chi-square test; the extent of dose reduction in different groups was compared using the Kruskal-Wallis nonparametric analysis of variance. Survival was plotted using the product-limit estimate of Kaplan and Myer and compared between groups using the log rank test or the test for linear trend for ordered groups [20].

## Results

Overall, 75 (68%) of the patients achieved CR at some time during chemotherapy, with a 95% confidence interval (C. I.) of 59%–77%. The response status of patients during the two phases of treatment is shown in Table 3. Eight pa-

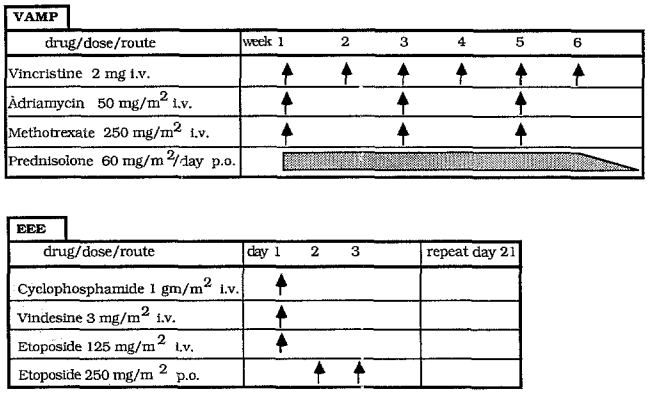


**Fig. 1.** Scheduling of treatment during induction phase (VAMP) and during non-cross-resistant consolidation phase (EEE). During treatment with methotrexate, urine was alkalinized by giving 2 g sodium bicarbonate q. d. s. orally for 4 days beginning 24 h before methotrexate. Folinic acid (15 mg) was given every 6 h orally for 3 days beginning 24 h after methotrexate

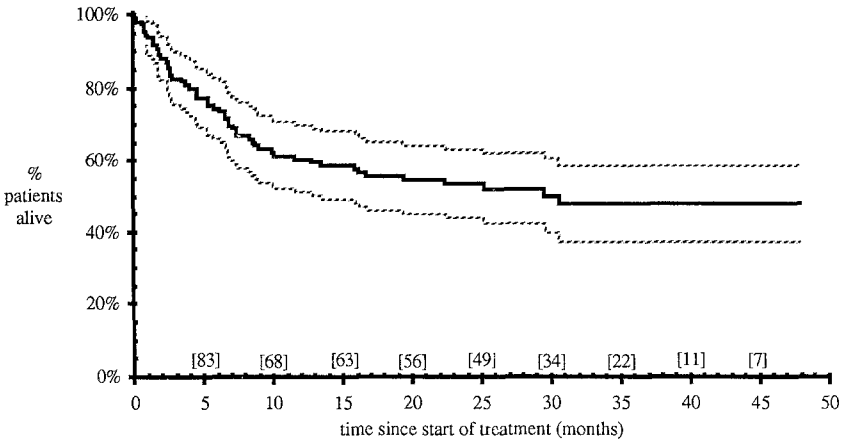


**Fig. 2.** Actuarial survival of all patients studied with 95% confidence limits. Numbers remaining at risk shown in brackets [*n*]

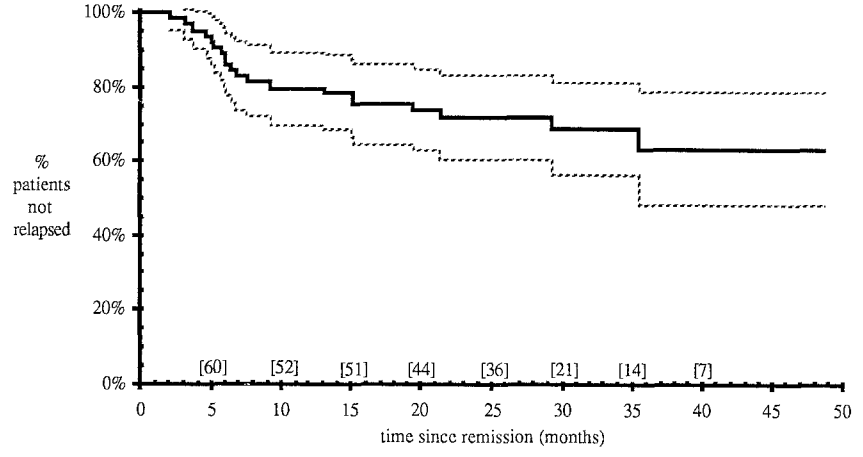


**Fig. 3.** Actuarial relapse-free survival, with 95% confidence limits, for patients achieving complete remission with chemotherapy. Numbers at risk shown in brackets [*n*]

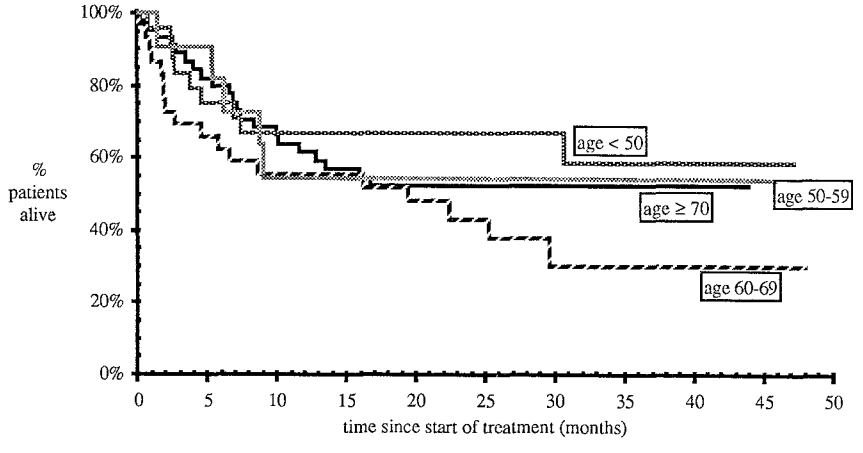


**Fig. 4.** Actuarial survival of all patients studied, divided by age. Age $<50$, $n = 45$; age 50–59, $n = 24$; age 60–69, $n = 30$; age $>70$, $n = 11$. ($\chi_1^2$ for trend $= 0.81$; $P = 0.37$)

tients who achieved CR with chemotherapy received additional radiotherapy (XRT) to sites of previous disease. Three who were not in CR at the end of chemotherapy were given XRT, and as a result one achieved CR.

The median follow-up was 34 months, with a minimum of 15 months. The median survival for all patients was 31 months (Fig. 2), with an actuarial 2-year survival for all patients of 53% (95% C. I., 44%–63%). Overall survival in different groups of patients was compared: there was no statistically significant difference for age (Fig. 4) or histology (Fig. 5). Patients with stage IV disease had worse survival prospects than other patients (Fig. 6), with a significant trend toward shorter survival in patients with more advanced disease ($P = 0.01$). Of the patients achieving CR 72% (95% C. I., 61%–83%) were free of relapse at 2 years (Fig. 3). There were, however, two late relapses beyond

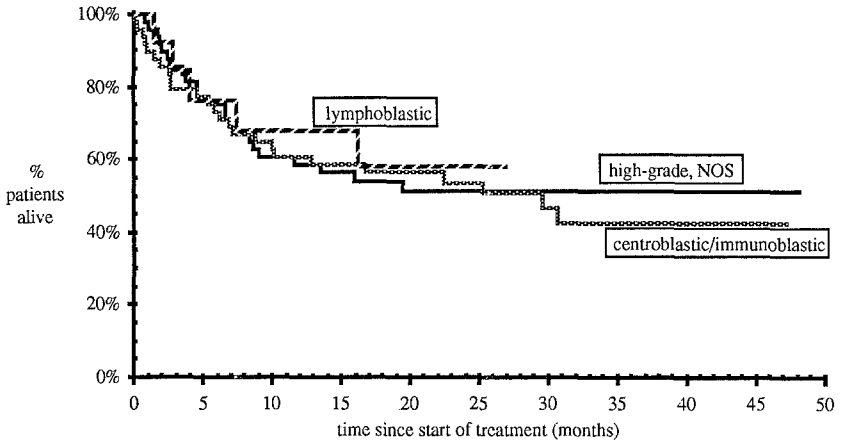


**Fig. 5.** Actuarial survival of all patients studied, divided by histological type. Lymphoblastic, $n = 13$; centroblastic/immunoblastic, $n = 49$; high-grade NOS, $n = 48$. ($\chi_2^2 = 0.326$; $P = 0.85$)

2 years, both in patients with stage IVB disease. Of 20 relapses, 17 occurred at sites of previous disease. The three sites of relapse not previously involved included two CNS relapses, one in a patient with lymphoblastic histology who had not received CNS prophylaxis.

The percentage of intended protocol dose received by patients is shown for each drug in Table 2; vincristine, vindesine, and methotrexate most often required dose reduction. Of 110 patients, 36 (33%) had no dose modifications during VAMP, and 39/87 (45%), no dose modification during EEE. Dividing patients into the age groups specified in Table 1 and comparing the extent of dose reduction in each group by the Kruskal-Wallis analysis of variance showed that older patients received significantly lower doses of vincristine (test statistic = 20.22; $P = 0.0002$), methotrexate (test statistic = 11.00; $P = 0.012$), cyclophosphamide (test statistic = 12.69; $P = 0.005$), and etoposide (test statistic = 10.91; $P = 0.012$). Of 110 patients, 60 (55%) completed VAMP with no delay, and 52/87 (60%) completed EEE with no delay. Twenty-three patients received no EEE, 17 because of death before EEE, four because of patient refusal, and two due to their withdrawal by their treating physician because of toxicity during VAMP. The number of cycles of EEE received ranged from one to eight, with 15 patients having less than three. Only one patient with lymphoblastic histology who achieved CR received prophylaxis against CNS relapse (intrathecal methotrexate and cranial XRT).

The dose-limiting toxicity during both phases of treatment was neutropenia, with neutrophil counts of less than $1.0 \times 10^9$/l occurring at some point during VAMP in 40 of 109 (37%) patients assessed, and at some point during EEE in 40 of 84 (48%) patients. Platelet counts $< 50 \times 10^9$/l occurred in only 6/107 patients during VAMP and 3/80 patients during EEE. Severe neuropathy was also rare (9/106 during VAMP). Moderate or severe mucositis was more common during VAMP (30/106 patients) than during EEE (3/77). Patients over the age of 60 had a higher incidence of severe neutropenia ($\leq 1.0 \times 10^9$/l) during VAMP (20 of 41 patients over 60, 20 of 68 patients under 60; $\chi^2 = 6.15$; $P = 0.046$) but no higher incidence of neutropenia during EEE nor of thrombocytopenia, mucositis, or neuropathy. Seventeen patients required treatment for proven or suspected septicemia while myelosuppressed.

Of 25 patients who died during treatment six died of progressive or unresponsive lymphoma. There were 12 deaths to which treatment contributed, 10 during VAMP and 2 during EEE. These comprised bacterial infections in eight patients, viral hepatitis in one, hemorrhage in one patient who had a low platelets count before chemotherapy commenced, and gastric perforation in two patients who had extensive gastric lymphoma. Five patients died of causes unrelated to disease or treatment – two of fatal pulmonary emboli, two of myocardial infarcts, and one of progressive renal failure that developed after completion of VAMP and prevented treatment with EEE. In two patients the cause of death could not be ascertained.

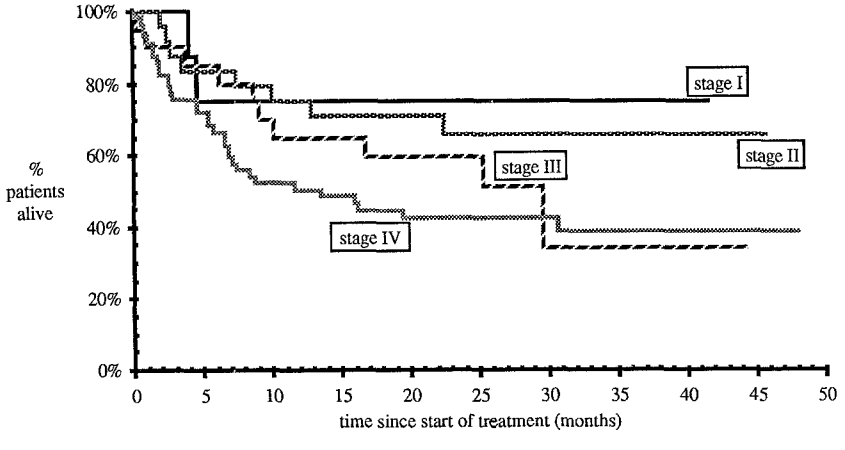


**Fig. 6.** Actuarial survival of all patients studied, divided by stage of disease. Stage I, $n = 8$; stage II, $n = 24$; stage III, $n = 20$; stage IV, $n = 58$. ($\chi_1^2$ for trend = 6.43; $P = 0.011$)

**Table 2.** Percentage of patients having dose reductions as shown

| Drug | Extent of dose received as a percent of full protocol dose | | | |
|---|---|---|---|---|
| | <50% | 50–75% | 76%-full | Full dose |
| Vincristine | 22 | 14 | 8 | 56 |
| Adriamycin | 6 | 19 | 17 | 58 |
| Methotrexate | 14 | 22 | 6 | 58 |
| Prednisolone | 4 | 4 | 5 | 87 |
| Etoposide | 8 | 15 | 24 | 53 |
| Vindesine | 16 | 12 | 14 | 58 |
| Cyclophosphamide | 3 | 17 | 16 | 64 |

## Discussion

The combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), devised soon after the introduction of doxorubicin (adriamycin) for the treatment of high-grade NHL, was one of the first to produce CR rates of over 50% [2, 14], becoming a widely used first-line regimen [27]. Many attempts have been made to increase the response rate produced by this regimen by the addition of further active but nonmyelosuppressive drugs such as bleomycin [13, 26] or methotrexate [8, 12], by intercalating radiotherapy [25], or by the addition of immunotherapy [15]. Most such regimens are still based on the administration of myelosuppressive drugs every 21 days or more; although there is some suggestion that these regimes are more effective than simple CHOP, long-term survival is generally no greater than 30%.

Other regimens with a greater number of active drugs [22], alternating non-cross-resistant combinations [10], or more frequent treatments [16] have produced higher remission rates and more long-term survivors than CHOP-based regimes. Most recently, the MACOP-B regimen [16] using short-course, weekly treatment has shown 2-year disease-free survival rates as high as 91%. While comparison between such uncontrolled studies is fraught with difficulty because differences in the patient groups can have a profound effect on results, at least one author has concluded that "there is absolutely no justification for the use of CHOP (alone) as first-line therapy in (high-grade non-Hodgkin's lymphoma)" [17].

The regimen described here was a development of VAP [3], the first intensive, weekly treatment schedule for high-grade NHL. The short but intensive initial, induction phase of treatment was followed by a non-cross-resistant combination with the aim of increasing CR rates and overall survival. In this study 49% of the patients were in CR at the end of the induction phase, a result similar to the 55% CR rate produced with VAP alone [3]. This does not exclude the value of the addition of methotrexate and may reflect differences in the populations under treatment. The fact that 18% of our patients achieved CR during EEE, together with the response to EEE in some patients showing disease progression during VAMP, suggests that the early switch to an alternative non-cross-resistant combination can increase the overall response rate. The CR rate with this regimen is comparable with that produced with ProMACE-MOPP or M-BACOD. Our results are not as good as those reported for MACOP-B; however, these studies cannot be compared, as the latter involved only 28% of patients aged over 60, only 33% of patients with stage IV disease, and no stage I patients. In the absence of stage-specific survival rates in most other studies, it is difficult to make further comparison. The M(m)-BACOD regimen, however, produces a 3-year survival probability of 0.55 for stage III or IV patients [21], a figure comparable to that in our study. The small number of stage I patients in this study all had bulky or abdominal disease inappropriate for treatment with radiotherapy. We feel it unlikely that the inclusion of these patients makes a significant difference to our overall conclusions.

Because of the increasing likelihood of toxicity or complicating medical conditions with age [1, 4, 5, 16], intensive combination regimes have been thought particularly inappropriate for elderly patients with high-grade NHL. However, nonintensive or "gentle" chemotherapy is likely to relieve symptoms for only a short time, and death from progressive disease usually follows rapidly [18]. In the present study the patients aged over 60, comprising 37% of the group, had a survival rate similar to that of younger patients. Routine dose reductions were not made but doses were attenuated in individual patients as clinically indicated. Although neutropenia during VAMP was more frequent in older patients, the overall incidence of toxicity was similar, suggesting that the lower doses of chemotherapy received by older patients were essentially equitoxic to those received by younger patients. This study would suggest that although older patients may require dose reduction, good results may still be achieved if the extent of this reduction is titrated to individual patients only to the extent needed to make the regime equitoxic to that of younger patients.

**Table 3.** Best response status of patients during VAMP with groups divided according to subsequent status

| Best status achieved during VAMP (110 patients received VAMP) | | Subsequent status of patients (23 received no EEE, 87 received EEE) | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | Died on VAMP | Alive no EEE | CR after EEE | PR after EEE | NR/PD after EEE | |
| CR | 54 | 5* | 4 | 45 | 0 | 0 | 54 |
| PR | 47 | 7 | 2 | 20 | 10 | 8 | 47 |
| NR/PD | 9 | 5 | 0 | 1 | 0 | 3 | 9 |
| Total | 110 | 17 | 6 | 66** | 10 | 11 | 110 |

CR, Complete remission; PR, partial remission; NR/PD, no response or disease progression
* All died in CR
** Four died in CR during EEE

Lymphoblastic lymphoma often has a rapidly progressive clinical course with early dissemination and frequent CNS involvement [23]. In this study no differences in survival were apparent when the broad histopathological groupings were compared. The median survival of patients with lymphoblastic lymphomas was similar to that of other patients. The intensive, weekly induction regimen may well be particularly appropriate for this rapidly proliferating tumor type. Further analysis of cell neoplastic phenotype is in progress to examine in more detail the nature of the lymphomas in this study and their relationship to the response to treatment and the outcome.

VAMP-EEE has therefore achieved a CR rate of 68% in patients with advanced high-grade NHL. Half of all patients entering this study were alive 3 years after starting treatment. This treatment can be given on an outpatient basis, with acceptable toxicity, even to patients in the 7th and 8th decade of life, and may be particularly effective in patients with lymphoblastic lymphoma. In the absence of any randomized comparisons, it is impossible to draw definite conclusions about the effectiveness of VAMP-EEE compared with other regimes, but it appears to be superior to the standard CHOP regimen. There is a pressing need for prospective, randomized studies comparing newer regimens with standard cyclical chemotherapy. We have continued to develop the concept of intensive, weekly chemotherapy and have taken it to its logical conclusion by devising a regimen in which the six most active drugs from VAMP-EEE are given on a weekly basis throughout [24]. We believe that the concept of weekly chemotherapy for high-grade NHL should now be tested more fully and have begun a prospective, randomized comparison between this new regimen (CAPOMEt) and the most widely used cyclical chemotherapy (CHOP-MTX).

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