ChlVPP IS AS EFFECTIVE AS ALTERNATING ChlVPP/ABOD IN ADVANCED STAGE HODGKIN'S DISEASE

HARALD HOLTE, OLAV MELLA, ERIK WIST, RAGNAR TELHAUG, EINAR HANNISDAL and ARNE FOSS ABRAHAMSEN

The purpose of the study was to evaluate and compare the efficacy and tolerability of two cytostatic regimens—chlorambucil, vinblastine, procarbazine and prednisone (ChlVPP) vs. ChlVPP alternating with doxorubicin, bleomycin, vincristine and dacarbazine (ABOD). One hundred eligible patients with stage IIIA–IVB Hodgkin's disease were randomized to either ChlVPP or ChlVPP alternating with ABOD. The complete response rate (CR) was 80% in both treatment groups. After a median follow-up time of 59 months, 42 (84%) of the patients in the ChlVPP-treated group were in CR compared with 39 (78%) treated with ChlVPP/ABOD. The estimated five-year overall and relapse-free survival rates were 87% and 74%, respectively, for the ChlVPP-treated patients and 76% and 73% for the ChlVPP/ABOD-treated patients. The ChlVPP regimen showed a slightly better subjective tolerance than the ChlVPP/ABOD regimen. The given dose intensity was very close to optimal, and equal for the two regimens.

Combination chemotherapy yields a long-term disease-free survival of 50 to 65% of all patients with advanced stage Hodgkin's disease (1, 2). Numerous efforts to improve these results have been made (1–4). There is also a general concern that late side effects such as secondary neoplasia as well as pulmonary and cardiac failure may be as important for long-term survival as minor improvements in complete remissions (1–11). Furthermore, the importance of dose intensity on remission rate and survival has been emphasized by several authors (3, 12).

MOPP chemotherapy was until the last decade the standard chemotherapy regimen in advanced Hodgkin's disease. After the published results (13) that the better-tolerated ChlVPP regimen was equally effective, all Norwegian Oncological Departments adopted this regimen as standard therapy in 1982. At the time of the initiation of the present study, Bonadonna et al. had claimed that alternating chemotherapy using MOPP and ABVD every other course gave superior results compared with MOPP therapy alone (14). In addition, by reducing the use of alkylating agents (mustine and procarbazine), the likelihood of secondary cancer and infertility may be reduced (6).

At the start of this study, the addition of radiotherapy to combination chemotherapy in advanced Hodgkin's disease was a controversial issue, and still is. Results from several centres support the use of radiotherapy to sites with initial bulky disease, usually the mediastinum, and to patients who do not obtain a complete response towards the end of the chemotherapy programme (3). The long-term toxicity after combined modality therapy especially in terms of secondary malignancies (5, 6) and pulmonary and cardiac toxicities are considerable (10, 11, 15) and should always be kept in mind when planning the therapy programme.

The present study was initiated as a Norwegian prospective randomized multicentre study to compare alternating combination chemotherapy using ChlVPP and ABOD with a 4-drug regimen—ChlVPP. The hypothesis tested in this study was that no difference existed between the two regimens concerning efficacy and tolerance. The main end-

From the Department of Oncology, The Norwegian Radium Hospital, Oslo (H. Holte, E. Hannisdal, A. Foss Abrahamsen), Department of Oncology, Haukeland Hospital, Bergen (O. Mella), Department of Oncology, University Hospital of Tromsø, Tromsø (E. Wist) and Department of Oncology, University Hospital of Trondheim, Trondheim (R. Telhaug).
Correspondence to: Dr. Harald Holte, Department of Oncology, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway, Telefax number: 22 93 58 08.

point of the study was overall survival. The secondary endpoint was relapse-free survival. Other important issues of the study were the tolerance to the two regimens and the given dose intensity. All responding patients were to receive eight courses in eight months. Radiotherapy would be given to sites of bulky disease at the initiation of chemotherapy, and in cases where complete remission was not obtained after six of the eight courses of chemotherapy.

Patient selection can confound the results even of randomized studies. As practically all patients with Hodgkin's disease in Norway in the given period were treated at one of the oncology departments contributing to the study, we believe a Norwegian multicentre randomized study including a population-based group of patients is less hampered by selection and in this respect yields important information.

Material and Methods

Four of the five regional oncology departments in Norway participated in this prospective randomized trial: The Norwegian Radium Hospital (75 patients randomized), Haukeland Hospital (14 patients), The Regional Hospital in Tromsϕ (11 patients) and The Regional Hospital in Trondheim (5 patients). The patients entered the study between February 1985 and February 1991 and were found eligible if they fullfilled the following criteria: A histopathological diagnosis of Hodgkin's disease classified according to the Rye nomenclature (16), stage III or IV disease according to the Ann Arbor classification, age between 15 and 70 years and no prior therapy for Hodgkin's disease. The patients were, however, found ineligible if they suffered from serious concurrent medical illness which would limit the administration of effective dose intensity and of life expectancy. Five patients were found ineligible because of wrong initial histopathological diagnosis (non-Hodgkin lymphoma four cases) and re-evaluation of staging classification (one case). No patients were lost to follow-up. Four patients refused further chemotherapy, two after one course and two after four courses of chemotherapy, because of side effects (nausea and vomiting). These four patients were included in the analysis. In total, 50 patients in each treatment arm were assessable.

Table 1

Patient's characteristics

Treatment group	ChlVPP	ChlVPP/ABOD	All patients
Number of patients	50	50	100
Sex (male/female)	34/16	35/15	69/31
Mean age (years)	36.8	32.4	34.6
Stage			
IIIA	13	18	31
IIIB	12	12	24
IVA	6	3	9
IVB	19	17	36
Histology			
Nodular sclerosis	24	26	50
Mixed cell type	21	16	37
Lymphocyte predominance	3	6	9
Lymphocyte depleted	0	0	0
Unclassified	2	2	4

The characteristics of eligible patients are listed in Table 1. The known risk factors were evenly distributed between the two treatment groups, with the exception of age in that a significantly higher proportion of patients receiving LVPP were in the 40–70-years age group.

The extent of the disease was assessed by clinical examination, x-ray of the chest, CT scans of thorax and abdomen and radionuclide scanning of liver and spleen. Bone marrow involvement was examined by bilateral bone marrow biopsies. Bipedal lymphography was performed if the above-mentioned examinations revealed disease involvement exclusively above the diaphragm. If uncertainty about infradiaphragmatic involvement persisted, staging laparatomy including splenectomy was performed.

Eight courses of chemotherapy were scheduled for each regimen. ChlVPP chemotherapy was administered according to the the original publication by Mc Elwain et al. (17): Chlorambucil 6 mg/m^2 orally (maximum of 10 mg/m^2 for a few patients) and procarbazine 100 mg/m^2 orally days 1–14, vinblastine 6 mg/m^2 intravenously day 1 and day 8 and prednisone 45 mg orally days 1–14. Patients randomized to receive ChlVPP/ABOD received ChlVPP as described on cycles 1, 3, 5 and 7, and ABOD on cycles 2, 4, 6 and 8. Patients were given 2 mg vincristine intravenously on day 1 and day 15 instead of vinblastine, as in the ABVD regimen, to avoid undue marrow toxicity (vinblastine was given in the ChlVPP regimen). With this exception, ABOD was administered according to Bonadonna et al. (18): doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2 and dacarbazine 375 mg/m^2, all substances administered intravenously on day 1 and day 14.

Standard criteria for response evaluation were used. Complete remission (CR) required a complete regression of all palpable or radiographic abnormalities. Residual tumours stable for at least two cycles were, however, considered to consist of only fibrous tissue. Response evaluation during chemotherapy was performed after two, four and six cycles of chemotherapy and consisted of repeating tests that had been found positive during pretreatment evaluation. The final evaluation was performed one to two months after completion of therapy. In cases of progressive disease after two cycles or later during therapy, the patients were given alternative chemotherapy (ABOD for patients randomized to ChlVPP, MIME (19) or CEP (20) for patients randomized to ChlVPP/ABOD), or in some cases radiotherapy. Further chemotherapy according

Table 2

Details of chemotherapy

Treatment group	ChlVPP	ChlVPP/ABOD	All patients
Number of patients given			
8 courses	40	40	80
6 or 7 courses	4	1	5
<6 courses	6	9	15
Reason for discontinuation of chemotherapy (number of patients)			
Death from lymphoma	0	3	3
Inadequate response	4	1	5
Death from infection	3	1	4
Leucopenia	0	2	2
Allergic reaction	1	1	2
Patient refusal	2	2	4
Total	10	10	20
Dose reductions or delay			
Optimal dose on time	39	30	69
Reduced or delayed dose	8	14	22
Reduced and delayed dose	3	6	9
Actual as % of intended dose intensity for patients given 6–8 courses of chemotherapy			
Chlorambucile max. 10 mg pr day	97.5	95.7	96.6
Chlorambucile 6 mg/m^2	95.5	94.2	94.9
Number of patients given various levels of intended dose intensity for those given 6–8 courses of chemotherapy			
70–80%	0	2	2
80–90%	2	3	5
>90%	42	36	78
Total	44	41	85

to the randomized regimen required at least a partial remission after four cycles. Patients having achieved a PR or CR after six cycles of chemotherapy were given two additional cycles.

Radiotherapy was given after chemotherapy according to the following three indications: Sites of bulky disease (tumour diameter greater than 6 cm or mediastinal width >1/3 of the thoracic diameter on an anterior-posterior x-ray film) at the initiation of chemotherapy, residual disease after six courses of chemotherapy or induction failures on first-line and second-line chemotherapy when considered the best therapy option for the patient.

The randomization was performed according to a simple randomization without stratification for any risk factors. Estimated overall survival time for individual patients is given from the date treatment was initiated until the date of the last observation or death. Relapse-free survival of patients having achieved a CR on induction treatment is given from date of treatment initiation to date of last observation or relapse. The overall survival (all deaths of any cause counted) and relapse-free survival curves were calculated by the product-limit method of Kaplan & Meier (21). The differences between the survival curves were tested by the logrank test (22). For two-way frequency tables, Fisher's exact test was used. All statistical analyses were performed with the BMDPC statistical software package (23).

All patients had sufficient data on dose and time schedule of the chemotherapy given to calculate the dose intensity. Fifteen patients who did not complete at least six cycles of therapy were excluded from the analysis of dose intensity (Table 2): Four patients refused further chemotherapy, four patients died early due to infection, and three patients had progressive disease. In four patients therapy was changed due to induction failure. The patients who suffered from an early death and early induction failures were all given adequate dose intensity during their initial cycles.

Actual and projected dose intensities were calculated for each drug and for each patient as described by Longo et al. (24). The chlorambucile dose was calculated also without capping the dose at 10 mg per day. Average percentage of projected dose intensity is given for the individual drugs and for the two regimens as a whole. As prednisone also was considered an important drug, it is included in the analysis, presuming the patient had taken the tablets as prescribed.

Results

Patients' characteristics

In all, 100 patients, 50 in each treatment arm, were evaluable and were included in the analysis. The two arms

of the study were well balanced as to patient characteristics, stage and histology (Table 1), with one exception: A significantly higher proportion of patients above the age of 40 had stage IV disease compared with the younger patient population (67% vs. 36%, $p < 0.003$). The median overall observation time was 59 months.

Toxicity and dose intensity of chemotherapy

Eighty patients (40 in each treatment arm) were given all eight planned courses, and, in addition, five patients were considered adequately treated with six or seven courses. The reasons for the patients not being given all eight courses are detailed in Table 2. It is noteworthy that only three patients died from tumour progression during the induction chemotherapy, and that none of these patients were in the ChlVPP arm. The two patients with allergic reactions had exanthema, probably due to chlorambucil, and were treated with the ABOD regimen later on.

Seventy-eight percent of the patients in the ChlVPP arm and 60% of the patients in the ChlVPP/ABOD arm were given scheduled doses at scheduled times (postponement of the entire course of 32 weeks by no more than one week, no dose reduction at all). Most dose reductions were, however, minor. Concerning the patients who were given six courses or more, the given dose intensity of the ChlVPP arm was 97.5% of the scheduled dose compared with 95.7% in the ChlVPP/ABOD arm (Table 2).

As for the majority of patients, a cut-off dose of 10 mg chlorambucil daily was practised; we have also considered the dose intensity for the patients who should have a higher dose in relation to their calculated body surface. The overall effect was minor, however, with a reduction of the relative dose intensity to 95.5% and 94.2% in the two arms. The number of patients with reduced dose intensity is also given in Table 2.

Radiotherapy

Standard indications for radiotherapy as part of the induction therapy were bulky disease at the initiation of therapy (14 patients) and partial remission after six chemotherapy courses (32 patients). Seven patients with a residual mass compatible with fibrous tissue at evaluation after six courses were not given radiotherapy, and they are all alive and in complete remission. No difference in the two treatment arms was observed in terms of the use of radiotherapy as part of the induction treatment.

Treatment results

At the end of therapy, 40 patients in each treatment arm achieved a CR (Table 3). All three early deaths in the ChlVPP arm were due to infections, while three of four early deaths in the alternative treatment arm died of progressive disease. All four fatal infections were in patients above 40 years of age with stage IV disease. At the last observation, 42 in the ChlVPP group (84%) and 39 in the ChlVPP/ABOD group (78%) were in complete remisssion (Table 3). One patient in each treatment group is alive with Hodgkin's disease. Only two of seven diseased patients in the ChlVPP-treated group succumbed from Hodgkin's disease, compared with seven of ten patients in the other treatment arm. Projected five-year overall survival is 87% for the ChlVPP group and 76% for the ChlVPP/ABOD group. The relapse-free survival rates with a median observation time of 59 months are 74% (ChlVPP) and 73% (ChlVPP/ABOD). A significantly higher proportion of older patients (40 years and above) received the ChlVPP regimen. There is, however, no difference between the two treatment groups when stratifying for age in the analysis (data not shown). Figures 1 and 2 show estimated overall and disease-free survival, respectively, for the two treatment groups. The difference in five-year overall survival was 13% (87% vs. 74%), giving a 95% confidence interval for the difference equal to 0–23%. ChlVPP and ChlVPP/ABOD seemed equally effective for both the stage III and the stage IV group of patients (Fig. 3a and Fig. 3b).

Table 3

Status at the end of therapy/at last observation (number of patients)

Treatment group	ChlVPP	ChlVPP/ABOD	All patients
CR	40/42	40/39	80/81
PR	6/0	6/1	12/1
SD	1/0	0/0	1/0
PD	0/1	0/0	0/1
Death from lymphoma	0/2	3/7	3/9
Death from infection	3/3	1/1	4/4
Death from other causes	0/2	0/2	0/4

Taking both treatment groups into consideration, patients with stage IV disease had a significantly poorer overall ($p < 0.001$), but not relapse-free survival rate (data not shown) compared with patients with stage III disease. This is explained by the fact that all early deaths occurred among the patients with stage IV disease. Interestingly, in this study with a documented high dose intensity, the elderly patients eligible for the study fared no worse than the younger ones. Despite all the early deaths from infections during chemotherapy-induced leukopenia that occurred in the older age group, there were no differences in the long-term overall and disease-free survival rates in the two age groups.

As reductions in dose intensity were due to prolonged leukopenia, tumour progression and patient compliance, we have not analysed the effects of dose on patient survival.

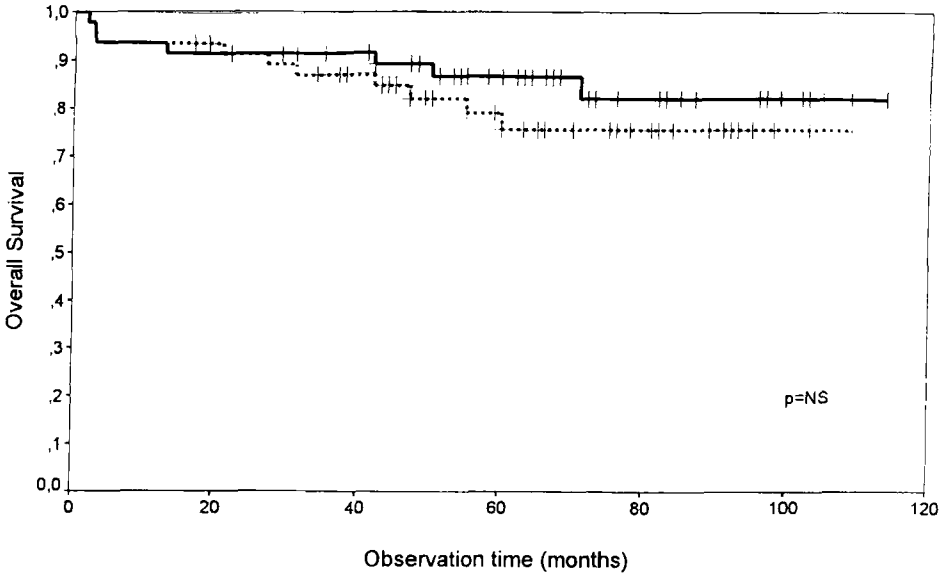

Fig. 1. Overall survival for 100 patients treated with ChlVPP stage III-IV Hodgkin's disease —— (50 patients) or with ChlVPP/ABOD – – – – – (50 patients), p = NS (not significant).

Discussion

As only 100 patients were included in the study, the results must be interpreted with caution. Thus, the power ($1-\beta$) of detecting a difference of 15% between the groups (i.e. 75% vs. 60% 5-year survival with type I error (α) = 0.05) is only 0.35. Nevertheless, our results indicate ChlVPP to be equally as effective as alternating ChlVPP/ABOD. Thus, there is no significant difference in CR rate at the completion of therapy or the five-year projected overall or disease-free survival between the two groups. In fact, only two patients receiving ChlVPP have died in direct relation to their lymphoma compared with seven patients in the group receiving alternating chemotherapy. This is, however, balanced by a slightly increased number of patients dying from infectious complications in the ChlVPP group (three patients versus one patient). All patients who died from infections were over 40 years of age and with stage IV disease.

Controversy still exists between centres treating advanced Hodgkin's disease for which a first-line regimen is preferred (12, 25). The issue entails several interacting questions including remission rates, disease-free and over-

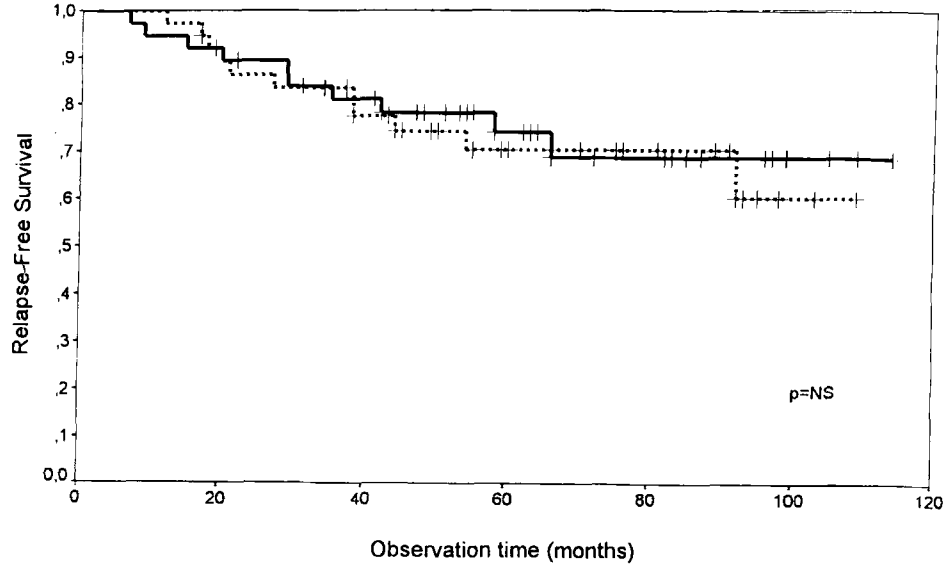

Fig. 2. Relapse-free survival for 100 patients treated with ChlVPP stage III-IV Hodgkin's disease ----- (50 patients) or with ChlVPP/ABOD – – – – – (50 patients), p = NS.

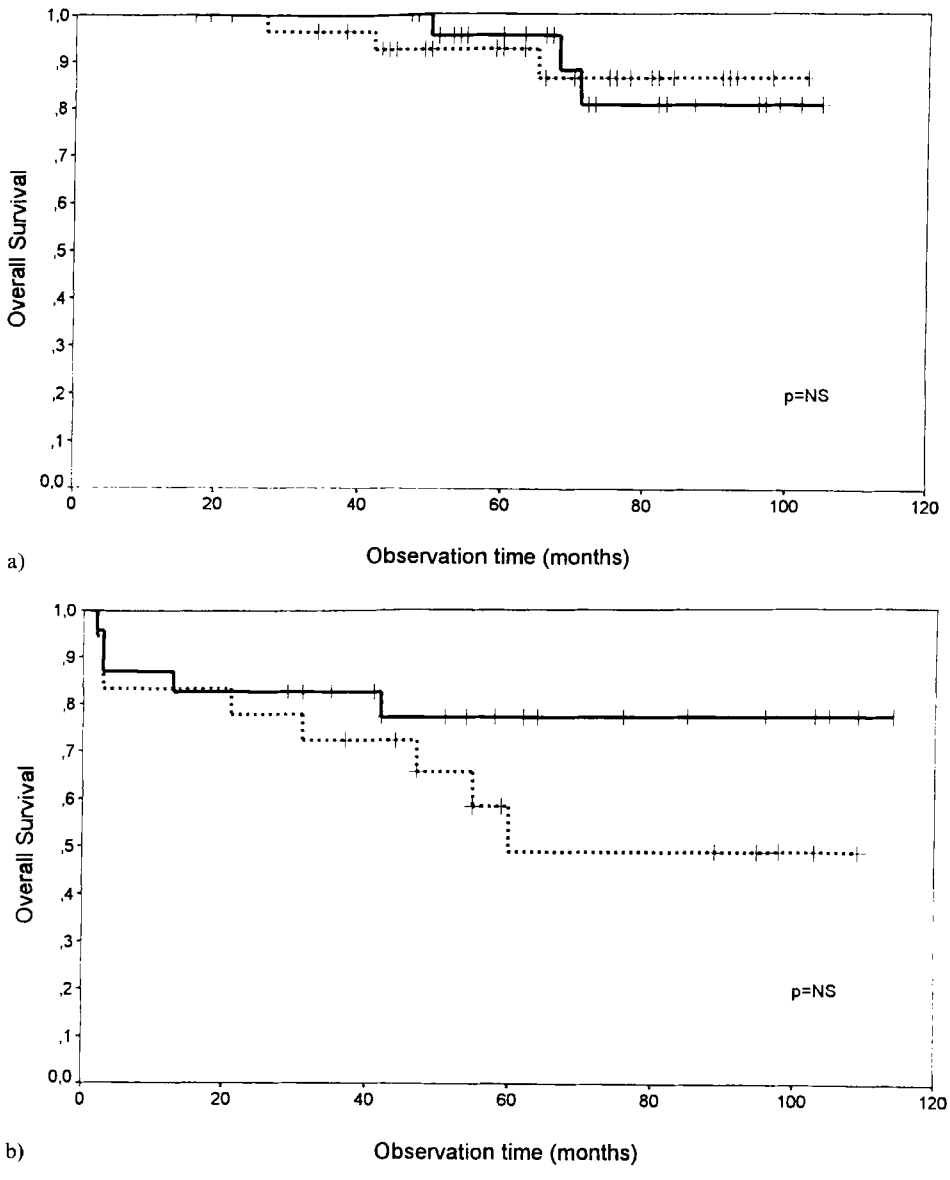

Fig. 3. Overall survival for a) 55 patients treated with ChlVPP stage III Hodgkin's disease xyz —— (25 patients) or with ChlVPP/ABOD – – – – – (30 patients), p = NS; and b) for stage IV with ChlVPP xyz —— (25 patients) or with ChlVPP/ABOD – – – – – (20 patients), p = NS.

all long-term survival, short-term and long-term side effects and the chance of inducing long-term remissions with a salvage regimen. Even randomized studies (14, 26–29) have not fully solved the question of the preferable four-drug regimen (MOPP-like or ABVD-like) or whether seven- to eight-drug regimens are better than a four-drug regimen. De Vita—the 'founder' of the MOPP-regimen which was the first regimen shown to cure advanced stage Hodgkin's disease in a considerable number of cases (15)—states that the one important factor determining the outcome is the dose intensity (2, 12). One logical reason for a combination of a seven- to eight-drug regimen in some studies (14) being superior to MOPP is that the use of alternating regimens or a hybrid regimen spreads out the toxicities because the dose of any single agent is reduced. Furthermore, as the main explanation for reducing the dose of the MOPP-regimen is the considerable nausea caused by mustine (12), we have used the ChlVPP-regimen at our institutions since the early 1980's. This is to our knowledge the first randomized trial comparing the ChlVPP regimen with an eight-drug regimen in advanced Hodgkin's disease.

The high dose intensity in both treatment groups documented in this study may be one factor explaining the favourable results. Both regimens were generally well tolerated. We thus consider ChlVPP to be preferable to MOPP, which is more difficult to administer in adequate doses due to excessive nausea and vomiting (13, 30). This study confirms that a four-drug regimen is equally effective to one including eight drugs.

The impact of radiotherapy in the first-line treatment cannot be confirmed from this study, but it is tempting to indicate that radiotherapy contributes to the high long-term survival. Other studies indicate that the recurrence rate is reduced by the addition of radiotherapy to bulky tumour sites (31–35). The role played by radiotherapy on the outcome of advanced stage Hodgkin's disease is presently addressed in the ongoing trial of the EORTC Lymphoma Cooperative Group (EORTC—20932).

In Norway, Hodgkin's disease is at present treated exclusively at the five departments of Oncology and Radiotherapy. As only one centre, covering 10% of the entire Norwegian population, did not participate, this study is less selective and basically population-based compared with all other similar studies. The median age of 34.6 years is comparable to or higher than that reported from other studies.

Several publications show that older patients with Hodgkin's disease have an inferior prognosis compared with younger patients (34, 36–42). In this study, only five patients above the age of 60 years were included. The survival rate for the 15–40 age group years is, however, comparable to that for the 40–70-years age group. Although the number of patients is limited, our study confirms previous results (42) showing that patients above the age of 60 years with Hodgkin's disease have an inferior bone marrow tolerance to curative combination chemotherapy. The ChlVPP regimen in particular seems too toxic for this age group, as three out of the four patients who died from infections during leukopenia had received this regimen. During later years, we thus adopted a less toxic regimen from the Swedish Hodgkin programme for this age group, in which doxorubicin, etoposide, vincristine and prednisone are alternated with ChlVPP at less intensive doses.

Results from The Norwegian Radium Hospital (6) and other institutions show that long-term side effects such as secondary leukaemias (43) and sterility are mainly attributed to the alkylating agents (44, 45), cardiomyopathy is due to antracyclins (9, 11), pulmonary toxicity is caused by bleomycin (7, 8, 10) and neuropathy is due to vinca alkaloids. Cardiopulmonary disease (10, 11) and secondary carcinomas (5, 6) are attributed to the use of combined chemotherapy and irradiation to the mediastinum. These serious long-term effects may be equally important for survival as minor differences in 5–10-year relapse-free survival. Many of the side effects may have a threshold level for each individual drug, which is an argument for the use of a seven- to eight-drug regimen. Some consider, however, that the secondary leukaemias and solid cancers together with the high probability of lifelong sterility in both males and females are more important than the cardiopulmonary toxicity of the ABVD regimen. Only one patient in our study developed another cancer (pulmonary carcinoma), and this lung cancer was diagnosed 2 years after the completion of first-line therapy. A longer follow-up is, of course needed to evaluate the risks of secondary cancers from the ChlVPP and ChlVPP/ABOD regimens.

The number of courses necessary to induce durable remissions is just as important as the choice of established drug combinations used in the primary treatment of Hodgkin's disease. The ongoing project on determining risk factors in Hodgkin's disease (International Prognostic Factor Project on Advanced Hodgkin's Disease) may indicate subgroups with better prognosis for which only four to six courses will be necessary. To reach firm conclusions, the optimal number of courses should then be tested in prospective randomized multicentre studies including a sufficient number of patients.

REFERENCES

1. Urba WJ, Longo DL. Medical progress: Hodgkin's disease. New Engl J Med 1992; 326: 678–87.
2. DeVita VT, Jr., Hubbard SM. Hodgkin's disease. N Engl J Med 1993; 328: 560–5.
3. Longo DL. The use of chemotherapy in the treatment of Hodgkin's disease. Semin Oncol 1990; 17: 716–35.
4. Bartlett NL, Rosenberg SA, Hoppe RT, Hancock SL, Horning SJ. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: A preliminary report. J Clin Oncol 1995; 13: 1080–8.
5. Van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: A 20-year follow-up study. J Clin Oncol 1994; 12: 312–25.
6. Abrahamsen JF, Andersen A, Hannisdal E, et al. Second malignancies after treatment of Hodgkin's disease: The influence of treatment, follow-up time, and age. J Clin Oncol 1993; 11: 255–61.
7. Lund MB, Kongerud J, Nome O, et al. Lung function impairment in long-term survivors of Hodgkin's disease. Ann Oncol 1995; 6: 495–501.
8. Cooper JAD, Jr., White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. Am Rev Respir Dis 1986; 133: 321–40.
9. Kantrowitz NE, Bristow MR. Cardiotoxicity of antitumor agents. Prog Cardiovasc Dis 1984; 27: 195–200.
10. Bauer KA, Skarin AT, Balikian J. Pulmonary complications associated with combination chemotherapy programs containing bleomycin. Am J Med 1993; 74: 557–63.
11. Minow RA, Benjamin RS, Lee ET, Gottlieb JA. Adriamycin cardiomyopathy—risk factors. Cancer 1977; 39: 1397–402.
12. DeVita VT, Jr. Is alternating cyclic chemotherapy better than standard four-drug chemotherapy for Hodgkin's disease? No. Important Adv Oncol 1993: 197–208.
13. Dady PJ, McElwain TJ, Austin DE, Barrett A, Peckham MJ. Five years' experience with ChlVPP: Effective low-toxicity combination chemotherapy for Hodgkin's disease. Br J Cancer 1982; 45: 851–9.
14. Santoro A, Bonadonna G, Bonfante V, Valagussa P. Alternating drug combinations in the treatment of advanced Hodgkin's disease. N Engl J Med 1982; 306: 770–5.
15. DeVita VT, Jr., Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970; 73: 881–95.
16. Lukes RJ, Craver LF, Hall TC, et al. Report of the nomenclature committee. Cancer Res 1966; 26: 1311.

17. McElwain TJ, Toy J, Smith E. A combination of chlorambucil, vinblastine, procarbazine and prednisolone for treatment of Hodgkin's disease. Br J Cancer 1977; 3: 7–10.
18. Bonadonna G, Zucali R, Monfardini S, DeLena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975; 36: 252–9.
19. Cabanillas F, Hagemeister FB, McLaughlin P, et al. Results of MIME salvage regimen for recurrent or refractory lymphoma. J Clin Oncol 1987; 5: 407–12.
20. Santoro A, Viviani S, Valagussa P, Bonfante V, Bonadonna G. CCNU, etoposide, and prednimustine (CEP) in refractory Hodgkin's disease. Semin Oncol 1986; 13: 23–6.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.
22. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35: 1–39.
23. Dixon WJ, Brown MB, Engelman L, Jennrich RI. BMDP Statistical Software Manual. 1990.
24. Longo DL, Duffey PL, DeVita VT, Jr., Wesley MN, Hubbard SM, Young RC. The calculation of actual or received dose intensity: A comparison of published methods. J Clin Oncol 1991; 9: 2042–51.
25. Connors JM. Is cyclic chemotherapy better than standard four-drug chemotherapy for Hodgkin's disease? Yes. Important Adv Oncol 1993: 189–95.
26. Longo DL, Duffey PL, DeVita VT, Jr., et al. Treatment of advanced-stage Hodgkin's disease: Alternating noncrossresistant MOPP/CABS is not superior to MOPP. J Clin Oncol 1991; 9: 1409–20.
27. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327: 1478–84.
28. Somers R, Carde P, Henry Amar M, et al. A randomized study in stage IIIB and IV Hodgkin's disease comparing eight courses of MOPP versus an alternation of MOPP with ABVD: A European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group and Groupe Pierre-et-Marie-Curie controlled clinical trial. J Clin Oncol 1994; 12: 279–87.
29. Radford JA, Crowther D, Rohatiner AZS, Ryder WDJ, Gupta RK, Oza A. Results of a randomized trial comparing MVPP chemotherapy with a hybrid regimen, ChlVPP/EVA, in the initial treatment of Hodgkin's disease. J Clin Oncol 1995; 13: 2379–85.
30. Druker BJ, Rosenthal DS, Canellos GP. Chlorambucil, vinblastine, procarbazine, and prednisone. An effective but less toxic regimen than MOPP for advanced-stage Hodgkin's disease. Cancer 1989; 63: 1060–4.
31. Gomez GA, Panahon AM, Stutzman L, et al. Large mediastinal mass in Hodgkin's disease. Results of two treatment modalities. Am J Clin Oncol 1984; 7: 65–73.
32. Crnkovich MJ, Leopold K, Hoppe RT, Mauch PM. Stage I to IIB Hodgkin's disease: The combined experience at Stanford University and the Joint Center for Radiation Therapy. J Clin Oncol 1987; 5: 1041–9.
33. Mauch P, Gorshein D, Cunningham J. Influence of mediastinal adenopathy on site and frequency of relapse in patients with Hodgkin's disease. Cancer Treat Rep 1982; 66: 809–17.
34. Pavlovsky S, Maschio M, Santarelli MT, et al. Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage I-II Hodgkin's disease. J Natl Cancer Inst 1988; 80: 1466–73.
35. Longo DL, Russo A, Duffey PL, et al. Treatment of advanced-stage massive mediastinal Hodgkin's disease: The case for combined modality treatment. J Clin Oncol 1991; 9: 227–35.
36. Austin-Seymour MM, Hoppe RT, Cox RS, Rosenberg SA, Kaplan HS. Hodgkin's disease in patients over sixty years old. Ann Intern Med 1984; 100: 13–8.
37. Specht L, Nissen NI. Hodgkin's disease and age. Eur J Haematol 1989; 43: 127–35.
38. Eghbali H, Hoerni Simon G, de Mascarel I, Durand M, Chauvergne J, Hoerni B. Hodgkin's disease in the elderly. A series of 30 patients aged older than 70 years. Cancer 1984; 53: 2191–3.
39. Walker A, Schoenfeld ER, Lowman JT, Mettlin CJ, MacMillan J, Grufferman S. Survival of the older patient compared with the younger patient with Hodgkin's disease. Influence of histologic type, staging, and treatment. Cancer 1990; 65: 1635–40.
40. Erdkamp FL, Breed WP, Bosch LJ, Wijnen JT, Blijham GB. Hodgkin's disease in the elderly. A registry-based analysis. Cancer 1992; 70: 830–4.
41. Enblad G, Glimelius B, Sundström C. Treatment outcome in Hodgkin's disease in patients above the age of 60: a population-based study. Ann Oncol 1991; 2: 297–302.
42. Peterson BA, Pajak TF, Cooper MR, et al. Effect of age on therapeutic response and survival in advanced Hodgkin's disease. Cancer Treat Rep 1982; 66: 889–98.
43. Van Leeuwen FE, Chorus AMJ, Van den Belt Dusebout AW, et al. Leukemia risk following Hodgkin's disease: Relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994; 12: 1063–73.
44. Viviani S, Ragni G, Santoro A, et al. Testicular dysfunction in Hodgkin's disease before and after treatment. Eur J Cancer 1991; 27: 1389–92.
45. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: A comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol 1995; 13: 134–9.