immunoassay measurement of estrogen receptors in human breast cancer: A European multicentric study. *Cancer Res* 1986, **46** (Suppl.), 4233s–4236s.
22. Pousette A, Gustafsson SA, Thörnblad AM, *et al.* Quantitation of estrogen receptor in seventy-five specimens of breast cancer: Comparison between an immunoassay (Abbott ER-EIA Monoclonal) and a [^{3}H]estradiol binding assay based on isoelectric focusing in polyacrylamide gel. *Cancer Res* 1986, **46** (Suppl.), 4308s–4309s.
23. Thorpe SM, Lykkesfeldt AE, Vinterby A, Lonsdorfer M. Quantitative immunological detection of estrogen receptors in nuclear pellets from human breast cancer biopsies. *Cancer Res* 1986, **46** (Suppl.), 4251s–4255s.
24. Andersen J, Bentzen SM, Poulsen HS. Relationship between radioligand binding assay, immunoenzyme assay and immunoistochemical assay for estrogen receptors in human breast cancer and association with tumor differentation. *Eur J Cancer Clin Oncol* 1988, **24**, 377–384.
25. De Lena M, Marzullo F, Simone G, *et al.* Correlation between ERICA and DCC assay in hormone receptor assessment of human breast cancer. *Oncology* 1988, **45**, 308–312.
26. Foekens JA, Portengen H, Van Driel J, Van Putten WLJ, Haije WG, Klijn JGM. Comparison of enzyme immunoassay and dextran-coated charcoal techniques for progesterone receptor determination in human breast cancer cytosols. *J Steroid Biochem* 1988, **29**, 571–574.
27. Piffanelli A, Fumero S, Pelizzola D, Berruto GP, Ricci L, Giovannini G. Protocollo del metodo con charcoal-destrano (DCC) per il dosaggio dei recettori dell'estradiolo e del progesterone nel tessuto neoplastico. *LAB* 1982, **9**, 13–21.
28. Agrimonti F, Berruto GP, Fornaro D, *et al.* Quality control for estrogen and progesterone receptor assay in human breast cancer: the influence of computation methods on intra and interlaboratory variability. *Tumori* 1985, **71**, 597–602.
29. Raam S, Vrabel DM. Preliminary appraisal of a PR-EIA kit for quantifying progesterone receptors in breast-cancer tissue. *Clin Chem* 1989, **35**, 339.
30. Senekjian EK, Press MF, Blough RR, Herbst AL, DeSombre R. Comparison of the quantity of estrogen receptors in human endometrium and myometrium by steroid-binding assay and enzyme immunoassay based on monoclonal antibodies to human estrophilin. *Am J Obstet Gynecol* 1989, **160**, 592–597.
31. Thorsen T, Tangan M, Stoa KF. Concentration of endogenous oestradiol as related to oestradiol receptor sites in breast tumour cytosol. *Eur J Cancer Clin Oncol* 1982, **18**, 333–337.
32. Saez S, Chouvet C. Influence of endogenous hormone levels on tumor estradiol and progesterone receptors. In: Leclerq G, Toma S, Paridaens R, Heuson JC, eds. *Recent Results in Cancer Research*. Berlin, Springer, vol. 91, 1984.
33. Drafta D, Priscu A, Neacsu E, *et al.* Estradiol and progesterone receptor levels in human breast cancer in relation to cytosol and plasma estrogen level. *J Steroid Biochem* 1983, **18**, 459–463.

Acknowledgement—This study was performed on behalf of Comitato Italiano per il Controllo di Qualità del Laboratorio in Oncologia.

Eur J Cancer, Vol. 27, No. 8, pp. 1002–1006, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Mechlorethamine, Vinblastine, Procarbazine and Prednisolone (MVPP) for Advanced Hodgkin's Disease

Margaret J. Harding, Laura J. McNulty, Jim Paul, Fred Lee, Alec Brown and Michael Soukop

Between January 1972 and October 1985, 60 patients with advanced Hodgkin's disease were treated with mechlorethamine/vinblastine/procarbazine/prednisolone (MVPP). The complete remission (CR) rate was 50%; the introduction of computed tomography in 1980 reduced the proportion of CR from 62% to 30% ($P = 0.017$) as a consequence of residual mediastinal abnormality of uncertain significance. With a median follow-up of 9 years, actuarial 5 and 10-year overall survival was 70% and 57%, respectively, with 79% and 65% free from Hodgkin's disease. Only age and pathological subtype influenced survival sufficiently to be of prognostic significance, though the effect of serum albumin, ECOG performance status and B symptoms on Hodgkin's disease mortality may have been clinically important.
Eur J Cancer, Vol. 27, No. 8, pp. 1002–1006, 1991.

INTRODUCTION

THE ADVENT of combination chemotherapy in the 1960s radically altered the prognosis of patients with advanced Hodgkin's disease [1]. Previously single agents had yielded at best a 5% 5-year survival [2], whereas the mechlorethamine/vincristine/procarbazine/prednisone (MOPP) regimen pioneered by de Vita has resulted in 10-year overall and disease-free survivals of 50% and 60%, respectively [3].

A British modification of the MOPP combination substituted vinblastine for vincristine to reduce the neurotoxicity [4]. The resulting MOPP regimen was adopted by several UK centres as standard treatment for Hodgkin's disease. We here report the mature data with MVPP from Glasgow Royal Infirmary.

PATIENTS AND METHODS

Between January 1972 and October 1985, 53 consecutive patients with advanced or bulky Hodgkin's disease and 7 with

Table 1. Characteristics of patients treated with MVPP

	Number	Percentage
Sex (M:F)	30:30	
ECOG performance status		
0	10	17
1	31	52
2	14	23
3	5	8
Histology		
Lymphocyte predominant	3	5
Nodular sclerosis		
Type I	14	23
Type II	6	10
Mixed cellularity	26	43
Lymphocyte depleted	11	18
Ann Arbor stage		
I A	0	3
B	2	
II A	4	18
B	7	
III A	10	57
B	23	
IV A	3	23
B	11	

relapse after radical irradiation received MVPP as initial chemotherapy. Patients' characteristics are shown in Table 1: their median age at diagnosis was 38 years (range 14–73). The original histology was reviewed by a single pathologist (F. L.) and reclassified according to currently accepted criteria [5] with particular reference to the subtype of nodular sclerosis [6].

Staging investigations were modified during the study in accord with contemporary practice. All patients had a full clinical examination, chest X-ray and bone marrow trephine. Bipedal lymphangiography was performed in 41, liver isotope scan or ultrasound in 9, and computed tomography (CT) of chest, abdomen and pelvis in 20. 26 patients presenting prior to 1980 underwent formal staging laparotomy and 12 of the other 34 had a percutaneous liver biopsy.

Both stage I patients had B symptoms and bulk mediastinal disease, 3 of 4 stage IIA lymphomas were > 10 cm in diameter, the fourth had relapsed within a previously irradiated area. Overall, 62% of patients had stage III B or IV disease.

Treatment comprised intravenous mechlorethamine 6 mg/m^2 and vinblastine 6 mg/m^2 on days 1 and 8, with oral procarbazine 100 mg/m^2 and prednisolone 40 mg on days 1–14: courses were delivered at 42-day intervals. Prior to 1978, maintenance treatment was given for 2 years at 3-monthly and 4-monthly intervals following the initial 6 courses.

Evaluation of response was based on clinical examination, chest X-ray, follow-up lymphogram films and, since 1980, CT. Complete remission (CR) required resolution of all clinical and radiological evidence of disease for more than 1 month. Residual abnormality on either criterion was included in the partial response (PR) category, together with the standard 50% or greater reduction in the sum of the products of 2 perpendicular nodal dimensions. Tumour regression less than 50% was considered a non-response.

In view of the controversy regarding the significance of residual radiological abnormality [7] the endpoints of this study are duration of remission and survival, both timed from the start of MVPP chemotherapy. Patient and tumour characteristics of potential prognostic significance were analysed by the Mantel–Haenszel logrank test. Kaplan–Meier estimates were used to produce survival curves which were terminated when only 5 patients remained at risk. Response rates pre-1980 and post-1980 were compared using Pearson's χ^2 test, without continuity correction.

RESULTS

Toxicity

There were 4 toxic deaths from neutropenic septicaemia, 3 of these occurring prior to 1977. Among the other 56 patients, there were only 4 episodes of significant infection (1 septicaemia, 3 localised). 10 patients had dose modifications (75% mechlorethamine and vinblastine) for WHO grade 3 or 4 myelosuppression.

1 patient died from acute non-lymphoblastic leukaemia 7.8 years from diagnosis, having received six cycles of MVPP and extensive salvage therapy including MOPP [4], doxorubicin/bleomycin/vinblastine/decarbazine [4], etoposide/vinblastine/doxorubicin/prednisolone (EVAP) [4] and extended-field irradiation. There were 3 other second malignancies in which treatment may have been implicated, including a gastric adenocarcinoma, anaplastic astrocytoma and salivary adenocarcinoma.

Most patients received prophylactic chlorpromazine and only 4 experienced protracted gastrointestinal toxicity. Alopecia did not exceed WHO grade 2 and symptomatic neuropathy was not observed.

Response

30 patients (50%) achieved a complete response. Prior to 1980 when response was assessed by clinical examination, chest X-ray and follow-up lymphogram films, 23 of 37 patients treated (62%) achieved a CR; however, the introduction of CT scanning in 1980 reduced this to 7 of 23 (30%): the difference is statistically

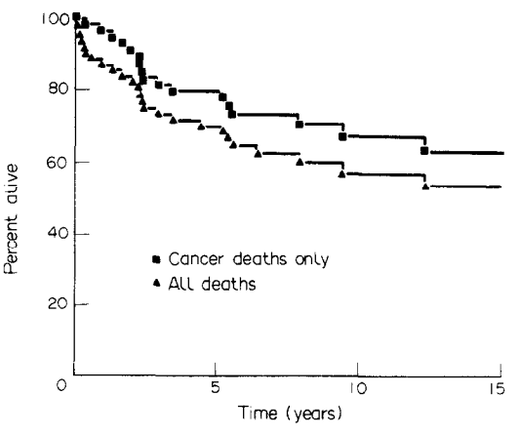

Fig. 1. Kaplan–Meier estimates of overall survival (all cause mortality) and Hodgkin's disease survival (non-cancer deaths censored).

Correspondence to M.J. Harding.
M.J. Harding, L.J. McNulty, A. Brown and M. Soukop are at the Department of Medical Oncology and F. Lee is at the Department of Pathology, Glasgow Royal Infirmary, Glasgow G4 0SF; and J. Paul is at the CRC Clinical Trials Unit, Beatson Oncology Centre, Glasgow, U.K.
Revised 1 May 1991; accepted 16 May 1991.

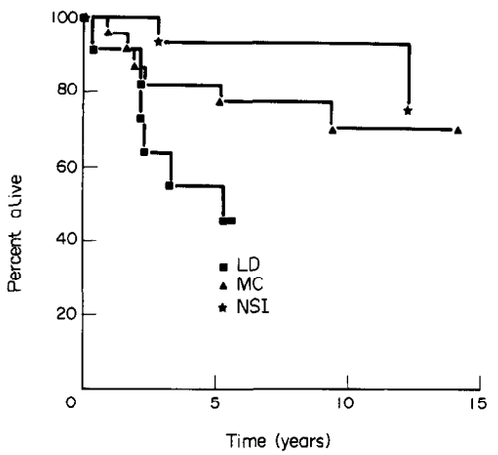

Fig. 2. Kaplan–Meier estimates of survival from Hodgkin's disease for type I nodular sclerosis (NSI, $n = 14$), mixed cellularity (MC $n = 26$) and lymphocyte depleted (LD, $n = 11$) histology. The differences are significant for NSI vs. MC and MC vs. LD ($P = 0.015$).

significant ($P = 0.017$). This anomaly arose because residual mediastinal CT abnormality in 9 patients, 7 of whom had bulk disease at this site at presentation, precluded assessment of response as complete.

22 patients (37%) achieved a partial remission. Further treatment of these patients comprised irradiation (4 cycles), alternative anthracycline-based chemotherapy (6) or both (3). There was no change in the residual radiological abnormality in the 7 patients whose disease was re-evaluated following second-line therapy.

2 patients had MVPP resistant disease and 5 died before remission status was fully evaluated.

Relapse

10 patients (33%) relapsed from CR at a median of 30 months (range 18–84 months). Durable second remissions (> 4 years) have resulted from an anthracycline-containing regimen alone ($n = 1$), in conjunction with irradiation ($n = 1$) and with the addition of high-dose chemotherapy and autologous marrow rescue ($n = 1$).

Table 2. Factors with some impact on survival (Hodgkin's disease mortality only)

	5-year survival (95% C.I.)	P
Pathology		
LD	54.5% (24.5–81.5%)	0.015
MC	81.8% (65.4–98.2%)	
NSI	92.9% (59.3–99%)	
Serum albumin		
≤ 40g/l	71.9% (56.1–87.7%)	0.054
> 40 g/l	93.7% (63 –99.1%)	
ECOG status		
0	100%	0.093
1	79.4% (64.4–94.4%)	
2/3	68.7% (45.5–91.9%)	
Symptoms		
A	100%	0.100
B	72.5% (58.3–86.7%)	

Table 3. Parameters of little prognostic significance in this patient population (Hodgkin's disease mortality only)

	5-year survival (95% C.I.)	P
Sex		
Male	74.1% (57.3–90.9%)	0.164
Female	85.2% (71.6–98.8%)	
Age		
≤ 40	82.9% (70.1–95.7%)	0.401
> 40	73.9% (53.7–94.1%)	
Nodal disease sites		
≤ 3	93.7% (63.0–99.1%)	0.451
> 3	73.7% (59.5–87.1%)	
Stage		
1/2	100%	0.304
3A	100%	
3B	63.8% (43.3–84.2%)	
4	75% (40.8–91.2%)	

7 of 22 patients (32%) achieving PR subsequently had progressive disease; their median duration of PR was 14 months (range 7–25 months). They include 6 of 9 patients who had no additional treatment, 1 of 6 who received alternative chemotherapy, none of 4 receiving irradiation and none of 3 receiving both.

There was a trend towards prolonged freedom from relapse for nodular sclerosing type I pathology ($P = 0.053$), female gender ($P = 0.055$) and serum albumin at presentation over 40 g/l ($P = 0.075$).

Survival

With a median follow-up of 9 years (range 4.5–17), 25 patients have died: 17 (28%) from Hodgkin's disease, 4 (7%) from neutropenic sepsis, 3 (5%) from a second malignancy and 1 from a cerebrovascular event.

Overall survival is illustrated in Fig. 1. The actuarial 5 and 10-year survival was 70% (95% C.I. 58–82%) and 57% (95% C.I. 44–71%), respectively. The superimposed Hodgkin's disease survival curve, censoring infective and incidental deaths gives an actuarial 5-year and 10-year survival from Hodgkin's disease of 75% and 65%, respectively.

Factors of prognostic significance for overall survival were age (> 40 yr vs. ≤ 40 yr, $P = 0.004$) and pathology (lymphocyte-depleted vs. mixed cellularity vs. nodular sclerosing type I $P = 0.023$). However, survival from Hodgkin's disease was unaffected by age ($P = 0.401$), as all toxic and incidental deaths occurred in the older age group (median 66 yr; range 47–72 yr).

Using conventionally accepted levels of significance, only pathology influenced survival from Hodgkin's disease (Table 2), the survival of patients with lymphocyte-depleted disease being significantly worse, and of those with nodular sclerosing type I disease being significantly better, than the survival associated with mixed cellularity pathology (Fig. 2). However, factors which may confer appreciable survival advantage (serum albumin > 40 g/l, ECOG performance status 0 or 1, absence of B symptoms do not reach levels of statistical significance in these patients (Table 2). Parameters of no demonstrable prognostic significance in this patient population are shown in Table 3. We could not analyse either absolute lymphocyte count, erythrocyte

sedimentation rate (ESR) or lactacte dehydrogenase (LDH) as data were incomplete.

DISCUSSION

Since the MOPP combination was introduced, it has been considered the gold standard against which other treatments have been compared. Although there have been few randomised comparisons of MOPP with its less toxic derivatives MVPP and ChlVPP, the regimens yield essentially similar results with 8-year actuarial survival of 60–75% depending on the relative proportion of stage II to stage IV patients included in each study (Refs 3, 8, 9 and 10 and this study). Our 10-year overall and Hodgkin's disease survival of 57% and 65% are very comparable with the original MOPP data where 50% and 60% of patients are alive and disease-free, respectively, at 10 years [3]. However, the most mature data indicate a continuing mortality beyond 8 years: in our patient population these were deaths from Hodgkin's disease occurring up to 6 years from initial relapse, though others report an increasing proportion of deaths from other causes which may be directly or indirectly treatment-related [3, 8].

During the period of this study, major changes in treatment strategy have taken place. Maintenance chemotherapy was abandoned [3] and a role for postchemotherapy irradiation to sites of initial bulk disease has been suggested though this hypothesis has not been subjected to a randomised trial [11]. CT has superceded most other radiological investigations for staging and response evaluation with an effect on CR rate which, in this study, reaches levels of statistical significance ($P = 0.017$). In retrospect, most if not all our long-term survivors who only achieved a PR might have been evaluated as unconfirmed or uncertain CR (CR[U]), a category recently defined at the Cotswold meeting [7]. In view of this controversy, factors of prognostic significance for achievement of CR or relapse-free survival have not been studied and remission status has been excluded from the analysis of prognostic factors for survival.

Factors evaluated for prognostic significance on the duration of remission, overall and Hodgkin's disease survival were based on the published literature in early [12, 13] and advanced lymphoma [3, 8, 9]. Glasgow data for ESR, LDH and absolute lymphocyte count were too incomplete for analysis.

In common with others, we found that the overall survival of older patients was inferior though different age discriminants have been used in the various studies (36 years [9], 40 years [ref. 15 and this study], 40 years [14]). However, in Glasgow this was entirely due to all 3 incidental and 4 toxic deaths occurring in patients over 40 years: in Manchester, fewer patients aged over 36 years achieved CR and their survival from CR was inferior [9], possibly reflecting an excess of intercurrent deaths. The interpretation of the BNLI data [15] was that, in early disease, survival from relapse was worse in older patients. Until the reasons for treatment failure in this group of patients are specified, rational treatment modification is not possible.

The relatively high incidence of mixed cellularity (43%) and lymphocyte depleted (18%) histology in the West of Scotland has been validated in an unpublished multicentre study (F. L.). The inferior survival associated with the lymphocyte-depleted subtype has been previously documented, albeit in a study where it comprised only 3% of the classifiable histology [8]. The prognostic gradation through mixed cellularity to type I nodular sclerosis is of note. Unfortunately, numbers of type II nodular sclerosis were too small to confirm the adverse effect of numerous pleomorphic Hodgkin's cells or areas of extensive lymphocyte depletion which characterise this subtype [6].

Serum albumin, performance status and B symptoms appear to have a major impact on survival in our study, although they do not reach conventional levels of statistical significance. However, they have been found to be of prognostic importance by others [3, 8, 14]. Furthermore, we could demonstrate no large effect of stage, tumour bulk, number of nodal sites or gender on overall or Hodgkin's disease survival, though they are significant in the experience of others [3, 8, 9, 12–15].

Such disparity between published series is not unexpected, as the improved survival of patients with Hodgkin's disease results in only a reasonable chance of detecting the very largest effects as statistically significant. For the same reasons of low statistical power, the probability of missing other important prognostic factors increases and a parameter should not be dismissed as unimportant because it fails to reach statistical significance, particularly in smaller studies.

Larger series also allow the development of prognostic indices based on several variables which alone may not appear of major importance. Such indices have been derived from patient populations including all stages of disease [14, 15] or restricted to those with III B and IV disease [16]. Unfortunately, the Glasgow data cannot be shown on this basis owing to incomplete data for ESR [14, 15] and absolute lymphocyte count [16].

It is hoped that assignment of individual patients to a good, intermediate or poor prognostic group will permit the development of randomised trials to address different questions within each category. The current issues for patients with the worst prognosis being the roles of early dose intensification with growth factor support and late intensification with very high-dose chemotherapy with autologous marrow rescue.

1. DeVita VT, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970, **73**, 881–895.
2. Jacobs EM, Peters FC, Luce JK, *et al.* Mechlorethamine HCL and cyclophosphamide in the treatment of Hodgkin's disease and the lymphomas. *JAMA* 1969, **203**, 392–398.
3. Longo DO, Young RC, Wesley M, *et al.* Twenty years of MOPP therapy for Hodgkin's disease. *J Clin Oncol* 1986, **4**, 1295–1306.
4. Sutcliffe SB, Wrigley PFM, Peto J, *et al.* MVPP chemotherapy regimen for advanced Hodgkin's disease. *Br Med J* 1978, **i**, 679–683.
5. Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. *Cancer Res* 1966, **26**, 1063–1081.
6. Bennett MH, MacLennan KA, Easterling MJ, *et al.* The prognostic significance of cellular subtypes in nodular sclerosing Hodgkin's disease: an analysis of 271 non-laparotomised cases (BNLI Report No. 22). *Clin Radiol* 1983, **34**, 497–501.
7. Lister TA, Crowther D, Sutcliffe SB, *et al.* Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. *J Clin Oncol* 1989, **7**, 1630–1636.
8. Olver IN, Wolf MM, Cruickshank D, *et al.* Nitrogen mustard, vincristine, procarbazine and prednisolone for relapse after radiation in Hodgkin's disease. An analysis of long-term follow-up. *Cancer* 1988, **62**, 233–239.
9. Wagstaff J, Steward W, Jones M, *et al.* Factors affecting remission and survival in patients with advanced Hodgkin's disease treated with MVPP. *Haematol Oncol* 1986, **4**, 135–147.
10. McKendrick JJ, Mead GM, Sweetenham J, *et al.* ChlVPP chemotherapy in advanced Hodgkin's disease. *Eur J Cancer Clin Oncol* 1989, **25**, 557–561.
11. Bonadonna G, Valagussa P, Santoro A. Prognosis of bulky Hodgkin's disease treated with chemotherapy alone or combined with radiotherapy. *Cancer Surv* 1985, **4**, 439–458.
12. Tubiana M, Henry-Amar M, Hayak M, *et al.* Prognostic significance

of the number of involved areas in the early stages of Hodgkin's disease. *Cancer* 1984, **54**, 885–894.
13. Specht L, Nordentoft AM, Cold S, *et al.* Tumor burden as the most important prognostic factor in the early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. *Cancer* 1988, **61**, 1719–1727.
14. Gobbi PG, Cavalli C, Federico M, *et al.* Hodgkin's disease prognosis: a directly predictive equation. *Lancet* 1988, **i**, 675–678.
15. Haybittle JL, Hayhoe FGJ, Easterling MJ, *et al.* Review of British National Lymphoma Investigation studies of Hodgkin's disease and development of prognostic index. *Lancet* 1985, **i**, 967–972.
16. Wagstaff J, Gregory WM, Swindell R, *et al.* Prognostic factors for survival in stage IIIB and IV Hodgkin's disease: a multivariate analysis comparing two specialist treatment centres. *Br J Cancer* 1988, 58, 487–492.

Acknowledgements—The authors wish to thank Mrs E. Posnett for meticulous record keeping over 17 years, Mrs J Beckett for secretarial assistance and the Cancer Research Campaign for financial support of Mrs L. McNulty and the Clinical Trials Unit.

Eur J Cancer, Vol. 27, No. 8, pp. 1006–1009, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

How Much Is Too Much? Folinic Acid Rescue Dose in Children with Acute Lymphoblastic Leukaemia

Joseph D. Borsi, Finn Wesenberg, Tore Stokland and Peter J. Moe

The effect of folinic acid rescue dose on the event-free survival of 71 children with acute lymphoblastic leukaemia was examined in a retrospective clinical study. All patients, diagnosed between 1 January 1980 and 1 January 1989, were treated according to the Norwegian Pilot protocol which included eight courses of high dose (6–8 g/m²/24 h intravenous infusion) methotrexate. Following the infusion, a uniform dose of 75 mg (at 36 h after the beginning of the drug infusion) and 15 mg (at 39–106 h) folinic acid rescue was administered to all patients, at predetermined intervals. The uniformity of the rescue dose resulted in distribution of dosages in the range of 38–140 mg/m² and 7.5–28 mg/m² for the different periods, respectively, when the dose was recalculated on the basis of the body surface area of the individual patients. The event-free survival of children receiving less or more than 15 mg/m² (75 mg/m²) rescue dose was compared. Although no significant difference was found, a tendency was observed for a lower risk of relapse in patients receiving less folinic acid. No major methotrexate-related toxicity was observed in the group of patients receiving the lower dose of rescue. These observations suggest that the reduction of folinic acid rescue dose below the generally accepted 12–15 mg/m² dose may increase the efficacy of high-dose methotrexate therapy while still remaining safe in preventing treatment-related toxicity. Prospective, randomised clinical trials are needed to examine the role of rescue as a determinant of effective exposure to methotrexate in patients receiving high-dose methotrexate treatment.
Eur J Cancer, Vol. 27, No. 8, pp. 1006–1009, 1991.

INTRODUCTION

DESPITE THE facts that intermediate and high-dose methotrexate/folinic acid rescue (MTX-FA) therapy seems to have an established role in the treatment of a number of malignancies in adults and in children, and pharmacokinetic parameters [systemic clearance, area under the curve (AUC) and steady state levels] determining systemic exposure to methotrexate have been shown to have prognostic importance in children with acute lymphoid leukaemia (ALL) and osteogenic sarcoma [1–3], no clinical data exist to show the role of folinic acid rescue as determinant of the efficacy of treatment with high-dose methotrexate.

In animal models, it has been shown that the effect of methotrexate may be compromised if the dose of folinic acid is excessive [4]. Recently, Browman *et al.* demonstrated the abrogation of both toxicity and antitumour effects of conventional (low-dose) methotrexate by low-dose folinic acid in adult patients in a double blind placebo controlled randomised clinical trial [5]. Here we report the results of a retrospective analysis in children with ALL; we examined whether such relationship between the dose of folinic acid and the effect of treatment could be determined following high-dose methotrexate therapy.

PATIENTS AND METHODS

Between 1 January 1980 and 1 January 1989, 71 patients older than 1 year of age and with non-B acute lymphoblastic leukaemia were treated according to the Norwegian Pilot Protocol in three

Correspondence to J.D. Borsi.
J.D. Borsi is at the Department of Pediatric Oncology, Second Department of Pediatrics, Semmelweis Medical School, Budapest, Hungary; F. Wessenberg is at the Department of Pediatrics, University of Bergen, Bergen; T. Stokland is at the Department of Pediatrics, University of Tromso; and P.J. Moe is at the Department of Pediatrics, University of Trondheim, 7000 Trondheim, Norway.