6. Bakri YN, Lee JH, Lewis GC Jr, Lublin FD, Danoff B. Meningeal carcinomatosis complicating gynecologic malignancies: a literature review and report of a case. *Obstet Gynecol* 1983, **38**, 1–4.
7. Behnam K, Aguilera AJ, Kornfeld M, Jordan SW, Hilgers RD. Meningeal carcinomatosis from an ovarian primary: a clinicopathological study. *Gynecol Oncol* 1983, **24**, 104–109.
8. Cooper KG, Kitchner HC, Parkin DE. Cerebral metastasis from epithelial ovarian carcinoma treated with carboplatin. *Gynecol Oncol* 1994, **55**, 318–323.
9. O'Boyle K, Wang Y, Swchartz E, Regl DL, Einzig A, Horwitz S. Development of two radioimmunoassays to detect paclitaxel in sera and in cerebrospinal, ascitic and pleural fluids. *Cancer* 1997, **79**, 1022–1030.
10. Freilich RJ, Seidman AD, De Angelis LM. Central nervous system progression of metastatic breast cancer in patients treated with paclitaxel. *Cancer* 1995, **76**, 232–236.

European Journal of Cancer, Vol. 34, No. 5, pp. 759–760, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10023-5

Phase II Trial of MINE as a Front-line Therapeutic Modality in Intermediate- and High-grade Non-Hodgkin's Lymphomas

I. Çelik, A. Kars, N. Güler, I. Barışta, G. Tekuzman, Ö. Özyılkan, M. Hayran and D. Fırat

Department of Medical Oncology, Hacettepe University Institute of Oncology, 06100 Sihhiye, Ankara, Turkey

NON-ODGKIN´S lymphomas (NHLs) are a heterogenous group of disease both in natural history and in their response to therapy. Patients with low-grade NHLs have usually an indolent but incurable disease in whom currently available therapeutic methods could offer only palliation. On the contrary, the vast majority of intermediate-grade and almost all high-grade NHLs exhibit an aggressive course, but also have a potential for cure when treated with combination chemotherapy. Nevertheless, the response of intermediate- and high-grade NHLs to conventional anthracycline combinations is still unsatisfactory and almost 50% of patients either do not achieve complete remission (CR) or eventually relapse after CR [1].

Identification of new drugs or combinations and incorporation of successful salvage regimens to the front-line treatments are the novel alternatives for the convenient management of aggressive NHLs [2, 3]. As the data of our previous study precluded no superiority of several first-line anthracycline combinations to each other by means of response and survival [4], we instituted a phase II trial of MINE (mesna, ifosfamide, mitoxantrone and etoposide) chemotherapy in previously untreated patients with intermediate- and high-grade NHLs to assess the response rate and the toxicity profile of this regimen.

Between 1990 and 1994, 32 patients with a mean age of 47.3 years (range 19–65) and a male/female ratio of 18/14 were prospectively recruited. There were 15 intermediate- and 17 high-grade NHLs according to the Working Formulation (excluding lymphoblastic lymphoma and adult T-cell leukaemia/lymphoma). After initial evaluation and staging procedures, patients received MINE chemotherapy consisting of ifosfamide 3 g/m^2 with mesna 3 g/m^2, i.v. (intravenous) 8 h infusion, on day 1; mitoxantrone 12 mg/m^2, i.v. 24 h infusion on day 1 and etoposide 100 mg/m^2, i.v. 1 h infusion, on day 1, to be repeated every 4th week. Patients achieving CR or partial remission (PR) after three courses received three more cycles to a total number of six.

The overall response rate was 65.7% (21/32 pts) (46.9% CR(15/32)+ 18.8% PR (6/32)) after a total of 148 and a median of 6 chemotherapy cycles. Median time to progression (TTP) was calculated to be 21.4 months (95% CI of 9.3–33.9) with a relapse rate of 62% after a median follow-up of 30 months (range 12–40). 4 unrelapsed patients (3 high- and 1 intermediate-grade NHLs) were long-term responders, after 30, 32, 36, and 40 months, with a possibility of cure. Univariate analysis of pretreatment factors disclosed shorter ($P < 0.05$) TTP in the presence of advanced stage, bulky disease and in patients with poor performance status (> 2, ECOG scale). Multivariate analysis revealed TTP to be significantly influenced by the presence of bulky disease and older age; i.e. patients with bulky disease had an 8.1-fold increased relapse risk compared with those without and increased age added a relapse risk of 1.07 per year.

The MINE regimen was generally well tolerated and no toxic death was encountered during or after chemotherapy courses. WHO grade 2–3 alopecia (92%), grade 2 nausea and/or vomiting (90%), grade 2–3 myelosuppression (74%) and grade 2–3 infectious complications (29%) were the most common toxicities. No hepatic, renal (including haemorrhagic cystitis) or cardiac toxicity was documented.

Mitoxantrone, a dihydroxyanthracenedione derivative, has been demonstrated to be an effective and better tolerated alternative in the salvage treatment of NHLs: mitoxantrone monotherapy providing a response rate of 40% [5], the combination of ifosfamide and mitoxantrone with a response rate up to 50% [3] and further addition of etoposide to the regimen yielding almost 70% response rate in previously treated patients with NHL [6]. Even though the data favours utilisation of mitoxantrone combinations as a first-line polychemotherapy for NHL, to date the results of this sort of trial have been lacking [2].

In this phase II trial, the characteristics of response regarding the pretreatment prognostic factors and the toxicity profile of front-line MINE regimen in patients with intermediate- and high-grade NHL have been documented. Despite the acceptable overall response rate obtained, certain limitations, such as the presence of a few long-term disease-free survivors and higher cost and toxicity, make a first-line MINE regimen unlikely to be an alternative to the conventional chemotherapy protocols. Nevertheless, future comparative phase III studies are warranted to draw more definitive conclusions.

Correspondence to I. Çelik.
Received 4 Aug. 1997; accepted 24 Aug. 1997.

1. Armitage JO. Treatment of non-Hodgkin's lymphoma. *N Engl J Med* 1993, **328**, 1023–1030.
2. Cabanillas F. Experience with salvage regimens at M.D. Anderson Hospital. *Ann Oncol* 1991, **2** (Suppl. 1), 31–32.
3. Case DC Jr, Santarelli MT, Carey RW, Anderson J, Gottlieb A. Phase II trial of ifosfamide/mesna and mitoxantrone in previously treated patients with non-Hodgkin's lymphoma: Cancer and Leukemia Group B study 8753. *Med Pediatr Oncol* 1992, **20**, 325–329.
4. Barişta I, Tekuzman G, Firat D, *et al.* Non-Hodgkin's lymphomas in Turkey: eighteen years' experience at the Hacettepe University. *Jpn J Cancer Res* 1994, **85**, 1200–1207.
5. Foss-Abrahamsen A, Lenner P, Hedenus M, *et al.* Mitoxantrone in the treatment of patients with non-Hodgkin's lymphoma. *Cancer Treat Rep* 1987, **71**, 1209–1212.
6. Rodriguez MA, Cabanillas FC, Velasquez W, *et al.* Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. *J Clin Oncol* 1995, **13**, 1734–1741.