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

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NON-OEDGIN’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/m² with mesna 3 g/m², i.v. (intravenous) 8 h infusion, on day 1; mitoxantrone 12 mg/m², i.v. 24 h infusion on day 1 and etoposide 100 mg/m², 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 (ECOG > 2, 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 dihydroxanthracenedione 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.