Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 410–412, 1994

0959–8049/94 $6.00+0.00

0959-8049(94)E0013-T

News: ESO Task Force Reports

Dose Optimisation and Intensification of Cytotoxics in Solid Tumours Supported by Haematopoietic Growth Factors

Thierry Le Chevalier

INTRODUCTION

THIS PAPER sets out to review the current evidence for the usefulness of cytotoxic drug dose or schedule modification in the treatment of patients with solid tumours. It goes on to address the role of haematopoietic growth factors (HGF) in the support of such strategies.

Currently, two haematopoietic growth factors, granulocyte colony-stimulating factor (rHuG-CSF) and granulocyte–macrophage colony-stimulating factor (rHuGM-CSF), are available for use in patients receiving myelosuppressive chemotherapy or autologous bone marrow transplantation (ABMT). Myelosuppression is the major dose-limiting toxicity of cytotoxic regimens, leading initially to the development of neutropenia and an increased risk of infection [1]. This in turn results in extended periods in hospital and necessitates the administration of broad-spectrum antibiotics. The need for dose reductions or delays between treatment cycles is a serious consequence of neutropenic infections, and might, possibly, have an adverse effect on treatment outcome. Schedule optimisation and limited dose escalation appear to be possible with CSF support. However, at present, there is minimal documented clinical evidence to support the usefulness of increasing the total dose administered, in terms of response rates, duration of response or survival. In this respect, CSFs are of importance in enabling the investigation of dose escalation with regard to treatment outcome.

Two issues must be addressed before considering the role of growth factors in treatment schedules for solid tumours. Firstly, does schedule optimisation improve response rates and survival, and secondly, how effective are escalated doses in terms of response rates and survival?

DOSE OPTIMISATION

On-schedule chemotherapy is often prevented due to the need for dose reductions or delays between cycles, as a result of haematological and non-haematological toxicity. Neutropenia and consequent infection are the first adverse effects indicating the need for dose reduction or delay.

Optimal delivery of chemotherapy is considered to be in place when the treatment protocol is strictly adhered to, in terms of the drug doses actually delivered, the number of treatment cycles received by the patient, and the time between treatment cycles.

A variety of retrospective studies have suggested that *ad hoc* reductions in dose intensity have a noticeable clinical impact. In patients receiving curative, as opposed to palliative, treatment, such dose reductions might have extreme adverse effects on response rate. For example, in patients with metastatic breast cancer, response rates have been shown to decrease considerably following small reductions in dose intensity [2]. However, in randomised trials designed to evaluate the effect of dose response in the treatment of breast cancer, there is generally a lack of definitive evidence to suggest improved clinical outcome and survival benefit following escalation of the standard dose.

A retrospective multivariate analysis of patients treated for limited small cell lung cancer (SCLC) demonstrated that the actual dose of cisplatin and cyclophosphamide received was often lower than the intended dose [3]. Overall survival was greater in patients receiving more than 80% of the intended dose in the first treatment cycle than in those receiving less than 80%. Differences in actual dose delivered over the subsequent five cycles had no effect on outcome, suggesting that it is initial chemotherapy that has an impact on survival. Indisputable evidence of the possible benefits of dose optimisation cannot be obtained from retrospective analyses, which can be biased in a variety of ways. For example, lower dose intensities than those prescribed may have been administered to patients with a poor prognosis. Prospective randomised studies are required to ascertain the true relationship between response, survival and dose intensity and as there is as yet no clinical evidence to support this view.

DOSE INTENSIFICATION

It is considered possible that dose escalation may improve response rates. Dose intensification can be achieved by reducing

Correspondence to T. Le Chevalier at the Institut Gustave-Roussy, Rue Camille Demoulins, 94805 Villejuif Cedex, France.
Revised 8 Nov. 1993; accepted 10 Jan. 1994.

the interval between treatment cycles or by increasing the dosage of one or more drugs in the treatment regimen.

The effect of modest dose escalation in the treatment of solid tumours is controversial. Although the majority of studies suggest benefits in ovarian, breast and testicular cancer, contradictory results have often been obtained. In terms of SCLC, data regarding the benefits of dose escalation are inconclusive.

However, in a recent phase III randomised trial involving 105 patients with limited SCLC [4, 5], two dosing levels of cyclophosphamide and cisplatin were used in the first cycle. The study demonstrated that a 20% higher initial dose of cyclosphosphamide and cisplatin resulted in a 25% increase in complete remission rate and a 50% increase in the duration of complete remission. Survival at 2 years was greater in the high dose group than in the low dose group ($P = 0.016$). This was confirmed when adjustment was made for prognostic factors ($P = 0.008$).

DOSE OPTIMISATION AND ESCALATION USING CSF SUPPORT

A variety of trials have assessed whether chemotherapy schedules can be adhered to more closely by supporting cytotoxic therapy with CSF administration. Although CSF support has enabled higher doses of chemotherapy to be achieved before the advent of haematological side-effects [6–9], the trials have not been adequately designed to ascertain whether increased dose intensity had a beneficial effect on response rate or survival.

Published trials relating to dose intensification tend to be non-standardised. In many studies the degree of dose intensification is not expressed quantitatively, nor is it made clear whether dose escalation involves a single dose, increased dose rate or increased total dose across all cycles.

Clinical studies of solid tumours suggest that the extent of dose intensification allowed by CSF support is limited, and may be in the order of 20–40% [10–12]. The reason is that at higher myelosuppressive drug doses thrombocytopenia and non-haematological toxicities become progressively more problematic than neutropenia. Because rHuG-CSF and rHuGM-CSF have no influence on platelet recovery, these cytotoxic effects cannot be reduced with CSF support.

Is the degree of dose escalation achievable with CSFs sufficient to translate into improved response rates and survival? Although efficacy of the CSFs in preventing neutropenia has been established, no randomised trials have related response rate and survival to these levels of dose escalation. Such studies would, by necessity, be large and expensive. For example, a study to demonstrate an anticipated 10% improvement would require 1000 patients; if the benefit was only 5%, over 3000 patients would be required [13].

STUDIES ON THE ROLE OF CSFs IN SUPPORT OF CHEMOTHERAPY

Chemotherapy with CSF support is being investigated in diseases including breast cancer and soft tissue sarcoma. Typical studies, both complete and underway, are summarised below.

Bronchud and colleagues [8] have indicated the effectiveness of chemotherapy in ovarian and breast cancer may be enhanced and the duration of treatment shortened by means of rHuG-CSF infusions following treatment with doxorubicin at 75–150 mg/m^2. At all doses, the neutrophil count returned to normal or above normal between 12 and 14 days after treatment, and this enabled chemotherapy to be given at 14-day intervals. In patients receiving doses of 125 and 150 mg/m^2, all tumours regressed rapidly, but at these doses there was also marked epithelial toxicity.

Other studies [14] have shown that rHuG-CSF support allows the interval between epirubicin (100 mg/m^2)/cyclophosphamide (830 mg/m^2) treatment cycles to be reduced from 22 to 13 days in patients with metastatic breast cancer. The increased dose intensity achieved by this means produced a clinical response rate of 94% and a complete response rate of 25%.

In advanced breast cancer, the optimal regimen of chemotherapy is undefined, hence the evaluation of new treatment schedules is of the utmost importance. With this in mind, a study [15] has been set up to evaluate the toxicity and efficacy of a modified FEC regimen (5-fluorouracil, epirubicin, cyclophosphamide) employing a high dose of epirubicin. The role of rHuG-CSF in the reduction of myelosuppression with this regimen will also be assessed in the study. Preliminary results suggest that rHuG-CSF support may enable increased doses of epirubicin to be delivered without causing neutropenia or infection.

Mitoxantrone shows promise in the treatment of advanced breast cancer. To determine the toxicities of intensive single agent mitoxantrone over repetitive cycles, a phase I dose escalation trial [16] has been initiated. To date, the doses used have been 16, 24 and 32 mg/m^2 every 21 days for six cycles. The drug was given in short intravenous infusions divided over days 1 and 2 of each cycle to minimise peak serum levels. A reference cohort of patients treated at the first dose level was given no rHuG-CSF following cycles 1 and 2. Subsequently, rHuG-CSF 5 mcg/kg/day subcutaneously was given from day 3 until neutrophil recovery. Findings in this trial suggest that adjunctive rHuG-CSF can limit the neutropenia associated with dose escalation, and that high doses can be given with good clinical tolerance. In view of these findings, further dose escalation studies of mitoxantrone are planned.

At the extreme end of dose intensification, rHuG-CSF and rHuGM-CSF have been employed with very high doses of chemotherapeutic agents and autologous bone marrow transplantation. Whether the reduction in morbidity using rHuG-CSF or rHuGM-CSF in this way translates into overall improved survival has yet to be determined.

In studies of carboplatin and etoposide with rHuG-CSF in the treatment of SCLC [17], the dose of carboplatin, given with a fixed dose of etoposide, could be increased to 650 mg/m^2. The indications were that this treatment regimen showed some activity in SCLC.

In soft tissue sarcoma patients receiving chemotherapy with rHuG-CSF support [18], addition of the CSF reduces the duration of neutropenia and enables a 25% dose intensification of MAID (mesna, doxorubicin, ifosfamide, dacarbazine) to be tolerated.

FUTURE PROSPECTS FOR CSF

In future trials, the tumours to target and dose regimens need to be identified. It is necessary to identify combinations with demonstrable anti-tumour activity and to ascertain which can most effectively be escalated before non-haematological toxicities come into play. So far, increases in dose allowed by CSF support have been modest. Dose response curves vary greatly from disease to disease, and benefits of CSF therapy will therefore have to be assessed individually for each type of tumour.

In conclusion, the body of evidence suggests that modest dose escalation can be beneficial in terms of outcome, although

additional trials demonstrating clinical significance have yet to be undertaken. The use of CSFs may allow dose optimisation and a limited degree of dose escalation in solid tumours. However, whether the increase in dose achieved, before non-haematological toxicity comes into effect, will be sufficient to improve response and survival is as yet unknown.

1. Bodey GP, Buckly M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute anaemia. *Ann Intern Med* 1966, **64**, 328–340.
2. Hryniuk WM. More is better. *J Clin Oncol* 1988, **6**, 1365–1367.
3. De Vathaire F, Arriagada R, de The H, *et al.* Dose intensity of initial chemotherapy may have an impact on survival in limited small cell lung carcinoma. *Lung Cancer* 1993, **8**, 301–308.
4. Le Chevalier T, Arriagada R, Pignon JP, *et al.* Initial chemotherapy (CT) doses have significant impact on survival in limited small cell lung cancer (LSCLC). Results of a multicentre prospective randomised study in 105 patients. *Proc ASCO* 1993, **12**, 327.
5. Arriagada R, Le Chevalier T, Pignon JP, *et al.* Initial chemotherapy doses and survival in limited small cell lung cancer. *N Engl J Med* 1993, **329**, 1848–1852.
6. Antman KS, Griffin JD, Elias A, *et al.* Effect of recombinant human granulocyte–macrophage colony-stimulating factor on chemotherapy-induced myelosuppression. *N Engl J Med* 1988, **319**, 594–598.
7. Gabrilove JL, Jakubowski A, Scher H, *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988, **318**, 1414–1422.
8. Bronchud MH, Howell A, Crowther D, Hopwood P, Souza L, Dexter TM. The use of granulocyte colony-stimulating factor to increase the intensity of treatment with doxorubicin in patients with advanced breast and ovarian cancer. *Br J Cancer* 1989, **60**, 121–125.
9. de Vries EGE, Biemsa B, Willemse PHB, *et al.* A double blind placebo controlled study with granulocyte–macrophage colony-stimulating factor during chemotherapy for ovarian carcinoma. *Cancer Res* 1991, **51**, 116–122.
10. Ardizzoni A, Sertoli MR, Corcione A, *et al.* Accelerated chemotherapy with or without GM-CSF for small cell lung cancer: a non-randomised pilot study. *Eur J Cancer* 1989, **26**, 937–941.
11. Scher H, Sidman AD, Bajourn, D, *et al.* Escalated M-VAC with G-CSF in urothelial cancer. *Proc ASCO* 1992, **11**, 199.
12. Sternberg CN, de Milder PHM, van Oosterom AT, Fossa SD, Giannarelli D, Soedirman JR. Escalated M-VAC chemotherapy and GM-CSF in patients with advanced urothelial tract tumours. *Ann Oncol* 1993, **4**, 403–407.
13. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat in Med* 1982, **1**, 121–129.
14. Piccart M, van der Schueren E, Bruning P, *et al.* High dose intensity chemotherapy with epi-adriamycin, cyclophosphamide and r-metHuG-CSF in breast cancer patients. *Eur J Cancer* 1991, Suppl. 2, S56.
15. Carmo-Pereira J, Henriques E, Costa FO. FEC (5-fluorouracil, epirubicin and cyclosphosphamide) as first line chemotherapy in disseminated breast carcinoma, with or without granulocyte colony stimulating factor (G-CSF): preliminary results. *Proc ASCO* 1992, **11**, A121.
16. Demetri GD, Harowitz J, McGuire BW, Meriea EA, Howard G, Henderson IC. Dose intensification of mitoxantrone with adjunctive G-CSF in patients with advanced breast cancer: a phase I trial. *Proc ASCO* 1992, **11**, A370.
17. Fujita J, Kamel T, Arilyoshi Y, Ikegami IL, Furuse K, Fukuoka M. Dose intensity study of carboplatin and etoposide with G-CSF in small cell lung cancer. *Proc ASCO* 1993, **12**, A1101.
18. Krakowski I, Bui B, Bonichon F, *et al.* Phase I-II trials on hematological tolerance and intensification of MAID chemotherapy with rG-CSF in locally advanced or metastatic soft tissue sarcoma patients. *Ann Oncol* 1992, **3**, suppl. 5, 4.

Acknowledgements—The European School of Oncology gratefully acknowledges an educational grant from Chugai-Rhone-Poulenc which made the meeting possible.

Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 412–414, 1994

0959–8049/94 $6.00+0.00

0959-8049(94)E0012-S

Cytokines in Clinical Cancer Treatment Trials: Methodological Aspects

U. Brennscheidt and A. Lindemann

INTRODUCTION

SEVERAL CYTOKINES have been incorporated into modern clinical cancer treatment. Their inclusion is based on direct and indirect anti-tumour effects, or on a supportive role with cytotoxic drug therapy. Clinical evaluation of these agents differs from that for chemotherapeutic compounds because dose–response relationships are not as clearly defined as for cytotoxic drugs, where a general premise still maintains that a higher dose corresponds to a more dramatic clinical response [1–3]. The optimal dose of cytokines may be unrelated to the maximum tolerated dose (MTD) as a network of interacting variables *in vivo*, controlled by different feedback systems, determines biological responses and therapeutic effects. Thus, phenomena of tolerance and priming may well be observed in this setting.

CYTOKINES AS ANTI-TUMOUR AGENTS

As with other drugs, it is essential to determine toxicity, optimal dose and schedule, as well as suitable routes of administration for cytokines with anti-tumour potential. With respect to safe handling in the clinical setting, it is also recommended to define the MTD. As the final pathway of cytokine-mediated anti-tumour effects will be completely different from one com-

Correspondence to U. Brennscheidt.
The authors are at the Department of Internal Medicine I, University of Freiburg Medical Center, Hugstetter Str. 55, D-79106 Freiburg, Germany.
Received 11 Nov. 1993; accepted 10 Jan. 1994.