A phase I/II trial of recombinant human granulocyte–macrophage colony-stimulating factor in the intensification of cisplatin and cyclophosphamide chemotherapy for advanced ovarian cancer

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Summary
A pilot study was undertaken in eight patients to assess the feasibility of recombinant human granulocyte–macrophage colony-stimulating factor (rH GM-CSF) support to intensify standard chemotherapy for advanced ovarian cancer using a shortened 15 day treatment interval. Only four patients completed the course of six cycles of cisplatin 75 mg m⁻² and cyclophosphamide 750 mg m⁻² with rH GM-CSF, 3–5 µg kg⁻¹ day⁻¹, days 3–14, but one of these suffered a toxic death on study. Another died of disease progression. There were two episodes of life-threatening infection (WHO grade 4), and three patients were withdrawn because of various rH GM-CSF-related problems. Although potentially affording some patients the hypothetical benefits of dose intensification, as well as the possible attraction of a shorter duration of chemotherapy, this regimen is not without problems.

Cisplatin combined with cyclophosphamide affords high response rates in ovarian cancer (Neijt et al., 1987). Both experimental and clinical studies have suggested a positive correlation between cisplatin dose intensity and response (Behrens et al., 1985; Levin & Hryniuk, 1986; Ngan et al., 1989). This has recently been confirmed by a prospective randomised trial (Kaye et al., 1992) which showed a survival benefit for a delivered dose intensity of cisplatin of 29.6 mg m⁻² week⁻¹ vs 16.3 mg m⁻² week⁻¹. While the shape of this dose–response curve remains uncertain, the further reduction of toxicity in pursuit of higher delivered dose intensity remains a major objective in the development of more effective chemotherapy for epithelial ovarian cancer. Attempts to exploit the differing dose-limiting toxicities of cisplatin and carboplatin by their use in combination are, as yet, inconclusive (Calvert, 1989; Lund et al., 1989; Muggia et al., 1990; Poole et al., 1992). Bone marrow suppression remains a major dose-limiting toxicity of any intensification programme and, while transfusion may reduce the effects of anaemia and thrombocytopenia, profound leucocytopenia nadirs predispose to infection and cause treatment delay.

Recombinant human granulocyte–macrophage colony-stimulating factor (rH GM-CSF) stimulates the growth and differentiation of multiple lineages of haemopoietic cells (Sieff et al., 1985; Metcalf et al., 1986) and increases peripheral blood neutrophil, monocyte and eosinophil counts. It therefore has the apparent potential to abrogate dose-limiting myelosuppression and permit safe treatment intensification. A reduction in the standard 21 day cycle interval for cisplatin 75 mg m⁻² and cyclophosphamide 750 mg m⁻² is one such approach. The objective of this study was to establish the feasibility of using rH GM-CSF support to achieve a 15 day dose interval for six cycles of this combination.

Patients and methods

Eight patients were recruited to the study, and their characteristics are shown in Table I. Entry criteria comprised historically confirmed epithelial ovarian carcinoma, age 18–70 years, ECOG performance status of <2, assessable residual disease, a white cell count (WCC) > 3.5 × 10⁹ l⁻¹, platelet count > 125 × 10⁹ l⁻¹, serum bilirubin <1.5 times upper normal, AST/ALT < twice the upper normal value, creatinine clearance > 50 ml min⁻¹. Ethical approval was obtained for the study, and all patients gave written informed consent prior to entry. Patients with a history of other malignancies, previous exposure to chemotherapy and/or cytokines and serious medical conditions were excluded. Response rates were assessed by UICC criteria, including CA-125 level (UICC, 1987).

rH GM-CSF (Schering/Plough) was administered subcutaneously, from day 3 to 14, at a dose of 3 µg kg⁻¹ day⁻¹. The first two injections were supervised in hospital, in order to detect known adverse reactions (Lieschke et al., 1989a). Haematological and biochemical profiles were checked thrice weekly for two cycles, and then weekly. The second cycle of therapy was started on day 15. In the event of an unacceptably low leucocyte or neutrophil count at the time of subsequent treatment, the dose of rH GM-CSF was increased to 5 µg kg⁻¹ day⁻¹, and chemotherapy restarted when the WCC rose above 3.0 × 10⁹ l⁻¹ and platelets above 100 × 10⁹ l⁻¹.

After the last cycle of chemotherapy, rH GM-CSF was continued for 15 days, or longer if required. In the event of the WCC exceeding 30 × 10⁹ l⁻¹ at any time, rH GM-CSF was stopped.

Results

A total of 44 cycles of chemotherapy were administered, 35 (80%) in combination with rH GM-CSF. Four patients completed six cycles of treatment under rH GM-CSF cover.

| Table I Patient characteristics | Number |
|--------------------------------|--------|
| Age 39–66 years (median 42 years) |        |
| Histology                      |        |
| Serous                         | 3      |
| Mucinous                       | 3      |
| Adenocarcinoma (unspecified)   | 2      |
| Stage                          |        |
| III                            | 7      |
| IV                             | 1      |
| Differentiation                |        |
| Moderate                       | 4      |
| Poor                           | 3      |
| Unknown                        | 1      |
| Residual tumour                |        |
| <2 cm maximum diameter         | 1      |
| >2 cm maximum diameter         | 7      |

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Three patients were withdrawn from study and the indications were: (i) fever and night sweats after the third cycle, resolving on cessation of rH GM-CSF; (ii) non-response to rH GM-CSF, requiring withdrawal from study after the second cycle; (iii) maculopapular rash and pruritus after the third cycle.

Delays were recorded in nine (26%) cycles of chemotherapy. No delay exceeded 8 days in any individual cycle. Causes included leucopenia/neutropenia (five cases), anaemia and thrombocytopenia (two cases) and suspected infection (two cases). Two patients required rH GM-CSF dose escalation to 5 μg kg⁻¹ day⁻¹ because of leucopenia.

Chemotherapy-associated toxicity is shown in Table II. Five patients required admission for blood transfusion, and one for platelet transfusion. Four patients had suspected infection, and these were life-threatening in two. In addition one patient died from resistant Staphylococcus aureus pneumonia and septicemia. This complicated neutropenia 8 days following the final cycle of treatment, and occurred despite prompt medical attention and intensive care. One patient developed cisplatin-induced nephrotoxicity after the last cycle of therapy, with a reduction in creatinine clearance to 35 ml min⁻¹. Only one patient developed symptoms of a mild sensory peripheral neuropathy.

Specific rH GM-CSF-related side-effects occurred in six patients (Table III). Two patients had transient elevations of alkaline phosphatase which returned to normal on cessation of rH GM-CSF. Two patients complained of fever and night sweats, and another two developed skin reactions at injection sites. One patient had an allergic reaction. This developed following the third course of therapy. The patient was admitted with a pruritic maculopapular rash which responded rapidly to intravenous Piriton and hydrocortisone. A WCC above 20 x 10⁹ l⁻¹ was recorded on at least one occasion in all patients with one episode of a level above 30 x 10⁹ l⁻¹. The effects on mean values of leucocytes, neutrophils and eosinophils are shown in Figure 1.

Dose intensity achieved

The planned duration of treatment was 75 days for six cycles. One patient died of disease progression immediately after her third cycle (without treatment delays), and four patients completed treatment with growth factor support in a total of 75, 78, 90 or 98 days. The one patient who completed chemotherapy in 75 days died from sepsis on day 8 of cycle 6. Records confirmed the duration of her previous nadirs at less than 48 h. Of the three patients who were withdrawn from rH GM-CSF, two received two cycles of therapy with rH GM-CSF support, after delays of just 1 and 3 days each. They subsequently completed chemotherapy in 91 days (five cycles only) and 126 days respectively. The last patient was on schedule when withdrawn immediately after her second cycle, and thereafter finished treatment in 128 days. Using the recommendations of Hryniiuk and Goodyear (1990) we calculate the received dose intensities as shown in Table IV.

Response and survival

Six of the eight patients achieved complete clinical responses. One of these (patient 2) was confirmed as a pathological CR at autopsy following septic death. Two patients had non-responsive disease, and one of these died during the study of disease progression. To date four patients have died at 7, 11, 12 and 13 months from entry. Two other patients are alive at 20 and 26 months from entry, though both have evidence of relapsed disease.

Discussion

This is the first report addressing the use of rH GM-CSF to intensify cisplatin and cyclophosphamide chemotherapy in ovarian cancer. Other studies have used rH GM-CSF sup-port for carboplatin treatment of patients with ovarian cancer (de Vries et al., 1991; Edmonson et al., 1992) and comparisons must therefore be qualified. deVries et al. (1991) undertook a randomised placebo-controlled trial and found a reduction in the severity of both neutropenia and throm-
boycotopenia with the addition of rH GM-CSF (3–6 μg kg⁻¹ day⁻¹ s.c.) to carboplatin 300 mg m⁻² and cyclophosphamide 750 mg m⁻² administered every 4 weeks. Edmonson et al. (1992) employed various doses and routes of GM-CSF administration with intensification of carboplatin/cyclophosphamide. They concluded that the most efficacious regimen was GM-CSF 5 μg kg⁻¹ s.c. every 12 h from days 6 to 3 prior to chemotherapy and days 1–14 with cyclophosphamide 1,000 mg m⁻² and carboplatin 600 mg m⁻² every 4 weeks. Tolerability problems encountered in both of these series were similar to our study. deVries et al. (1991) reported local skin reactions at injection sites in all patients, resulting in the withdrawal of two patients. Another two patients developed a generalised rash with itching following the first or second cycle of treatment. In their study no fever or hypotensive reactions were observed. Edmonson et al. (1992) detected these, and with higher doses encountered the more serious side-effects of pleuritis, pericarditis, atrial fibrillation and pulmonary reactions. Two of three patients receiving GM-CSF at 10 μg kg⁻¹ every 12 h on days 6 to 3 prechemotherapy and days 1–14 developed exfoliative dermatitis. This regimen was abandoned because of such severe toxicity. In Edmonson et al.'s series of 30 patients with 'ovarian carcinoma' only ten completed therapy as planned. One patient was withdrawn because of GM-CSF-induced pulmonary reaction, three because of disease progression and one patient refused further treatment after the third completed cycle. Five patients completed four or five cycles of treatment but no indication is given as to why they had not completed a full course as planned. Ten patients were withdrawn from study, although it is not stated whether this was toxicity related.

Myelosuppression is a major obstacle to dose intensification of chemotherapeutic regimens. Maintenance of neutrophil count is important as severe infection in neutropenic patients increases particularly at counts below 0.5 × 10³ l⁻¹ (Bodey et al., 1966). Severe (WHO grade 3/4) neutropenia was encountered in three patients in this series, and one patient (number 2) died of staphylococcal sepsis on day 8 of her sixth cycle of treatment. Transient leucopenia was expected after each dose of rH GM-CSF-covered chemotherapy (Devereux et al., 1987), but it had been hoped that the risks of serious infection might be low, reflecting both the short duration of the nadir and the relative rarity of concurrent oral mucositis with these drugs. It is notable that in patient No. 2 recorded WCC nadirs had been of less than 48 h duration prior to her fatal sixth cycle.

Another striking event was the failure to obtain a WCC increment in one patient. Unfortunately, no information is available about the possible presence of neutralising antibodies, although this is considered a rare phenomenon (Gribben et al., 1990).

rH GM-CSF side-effects such as pyrexia and sweats (and raised WCC) (Lieschke et al., 1990) pose a diagnostic dilemma for the physician, mimic sepsis, and often result in patients' admission, investigation and empirical antibiotic treatment, and on occasion cause chemotherapy delay. In this series two patients had delayed treatment because of suspected infection, although no organism was identified on routine investigations. One patient requested withdrawal from the trial because of night sweats, after an increase in dose to 5 μg kg⁻¹ day⁻¹. As has been reported elsewhere (Lieschke et al., 1989) two patients developed erythematous local reactions at their injection sites.

rH GM-CSF has occasionally been reported to have a beneficial effect on platelet production in both animal and human studies. In mice, platelet recovery after irradiation was enhanced by the introduction of GM-CSF (Tanikawa et al., 1989), and two clinical series allude to higher platelet counts and a reduction in platelet transfusion requirement following rH GM-CSF (Gianni et al., 1990; Edmondson et al., 1992). We did not detect any such effect. Only one patient had increased platelet counts. We suspected this was tumour induced, and related to disease progression. Haemoglobin concentrations fell across treatment, with transfusions necessary in five patients. As expected, marked eosinophilia occurred in all patients, reflecting increased eosinophil production and cellular half-life (Owen et al., 1987).

In such a small series response and survival rates merit little comment, but no obvious adverse effects on tumour growth were seen.

This preliminary series shows that rH GM-CSF can be used to support intensification of combined cisplatin/cyclophosphamide chemotherapy. The average dose intensity achieved was 28 mg m⁻² week⁻¹, which falls short of the intended 37.5 mg m⁻² week⁻¹. This compares favourably though with previous studies from this group, which demonstrated that for an intended dose intensity of 25 mg m⁻² week⁻¹ (cisplatin 75 mg m⁻² and cyclophosphamide 750 mg m⁻² every 3 weeks), the actual average dose intensity achieved was 20.3 mg m⁻² week⁻¹. It is therefore possible to support intensification of delivered dose using rH GM-CSF.

However, the use of rH GM-CSF is not without problems. In 3/8 patients rH GM-CSF was withdrawn because of fever and night sweats, non-response to chemotherapy and the development of an allergic skin reaction. rH GM-CSF in this series did not entirely prevent serious infections, and there were two episodes of life-threatening sepsis and one death from Staph. aureus pneumonia and septicaemia.

Interestingly, some patients elected to persist with rH GM-CSF despite troublesome local skin reactions, clearly motivated by the prospect of a reduction in the overall duration of their chemotherapy. This demonstrates the importance of including a detailed quality-of-life assessment in future studies. It seems plausible that higher doses of rH GM-CSF may be required to condense cycle intervals further, which presumably will increase the incidence of local adverse reactions, fevers and sweats.

Because of the problems that we have encountered and the small increase in average delivered dose intensity obtained, we have no immediate plans to embark on further intensification studies employing rH GM-CSF. Were we to pursue this further the most informative setting might be a randomised phase II study, against the same schedule supported by rH GM-CSF, incorporating quality-of-life end points.

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