Eur J Cancer, Vol. 29A, Suppl. 5, p. S1, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00
Pergamon Press Ltd

Introduction

THE FOLLOWING six papers describe brief updates of work being performed by European and U.S.A. investigators utilising growth factors to improve dose-intensive therapy for malignant disease, as well as interleukin-2 (IL-2), interferon-alfa (IFN-α) and retinoids in combination with more conventional types of chemotherapy. Each of these trials describes ongoing work and the results are thus necessarily preliminary in nature. Nonetheless, they are intriguing in that they provide evidence for improved response rates with combinations of interferon-alfa and IL-2 plus chemotherapy in melanoma and renal cell carcinoma as well as combination trials of retinoic acid and interferon and dose intensification efforts in the lymphomas and bone marrow transplants.

The first paper by D. Khayat *et al.* describes efforts by their group to improve chemoimmunotherapy of metastatic melanoma. 39 patients with melanoma were treated with a combination of cisplatinum, IL-2 and IFN-α2a. 33 of these patients had received prior chemotherapy and 17 had received prior INF. They describe a high overall response rate of 54% with 13% complete and 40% partial responses, despite the fact that these patients had been previously treated. Their median survival was 47 weeks, with more than a 48-week median survival among the responding patients. Despite the fact that the combination did have reversible renal toxicity, more than 70% of the planned platinum and IL-2 doses, and 50% of the planned IFN doses were achieved among the treated patients. All patients showed benefits early with no benefit found for maintenance therapy with the same regimen, and relapses occurred relatively early within a 3-month time period. These data demonstrate additive benefits of platinum, IL-2 and IFN-α, although I would disagree with the authors' conclusions that they confirm synergistic activity. Nonetheless, this high overall response rate and 13% complete response rate is certainly encouraging in refractory melanoma.

The second paper by Jens Atzpodien summarises his group's efforts in renal cell carcinoma treated with IL-2, IFN-α and 5-fluorouracil (5-FU). The 5-FU in this particular regimen was given by bolus rather than by continuous infusion. The overall response rate identified by this group was 48.6% with a range of 32 to 66%, and 11.4% of these responses were complete. Regression occurred in most tissues including bony metastatic disease and thus this regimen compares favourably with an overall response rate to IFN-α alone of 16% and IFN-α combined with IL-2 of 28%. No severe 5-FU mucositis was noted and the toxicities were thus relatively mild and easily tolerated in the outpatient setting. Although these results probably represent 5-FU-mediated response rates, nonetheless it is encouraging that this combination can be given without major toxicities and may be optimising responses to IL-2 and IFN.

In the third paper prepared by Scott Lippman *et al.*, they describe an update of the rationale and early responses of squamous cell malignancies to retinoic acid in combination with either IFN-α or IFN-γ. The rationale is based on *in vitro* antiproliferative additive activity of these compounds and is described with the suggestion that both IFN and retinoic acid are capable of reversing premalignant skin conditions. Lippman cites their own clinical trial in cutaneous squamous cell carcinoma in which they have achieved a 68% overall response rate among 28 patients, with 7 of 19 responding patients achieving complete responses. These response rates thus compare quite favourably to those achieved with cisplatinum which are in the 60–70% range. Other data, more preliminary in nature, were described for cervical carcinoma in which a 50% complete response + partial response rate with 4 complete responses was obtained, and Lippman goes on to describe their current trial in cervical carcinoma combining retinoic acid, IFN-α and radiation therapy.

The fourth paper by Trillet-Lenoir *et al.* essentially sets the stage for understanding the issue of dose intensity in the lymphomas with the description of both the methods of dose intensity calculation, as well as early results in Hodgkin's disease dose intensification with granulocyte colony-stimulating factor (G-CSF).

In the fifth paper, Bronchud reviews the potential for haematological growth factors and dose intensity in Hodgkin's disease as well as non-Hodgkin lymphoma. This manuscript represents an excellent review of the question of dose intensity in the lymphomas and addresses the following two important questions: (1) The advantages of using Hodgkin's disease as a model for studying dose intensity, and (2) the disadvantage of utilising intermediate and high-grade non-Hodgkin lymphomas as the model. Bronchud goes on to present a persuasive argument for studying dose-intensity questions in Hodgkin's disease.

The final paper by L. Kanz *et al.* describes combinations of haematopoetic growth factors and peripheral blood stem cells in achieving dose intensity in patients undergoing autologous bone marrow transplantation. Utilising a regimen of intensive vinblastine, ifosfamide and cisplatinum followed by interleukin-3 combined with granulocyte–macrophage colony stimulating factor (GM-CSF) and peripheral blood progenitor cells primed with G-CSF, their data tend to argue that optimum neutrophil and platelet recovery requires both G-CSF-primed peripheral blood progenitors as well as growth factors, even given the combination of GM-CSF and IL-3. These data, therefore, suggest that this haematopoetic growth factor combination is inadequate for either platelet or neutrophil recovery, and support the contention that peripheral blood progenitor cells may be necessary for optimising dose-intensive therapies in autotransplantation.

Overall, the data from these studies tend to raise intriguing questions regarding the role of cytokine integration with chemotherapy in dose intensity. It is evident from the manuscripts assembled here that cytokines are playing an increasingly important role in combination therapy and that, in the future, novel combinations and newer cytokine strategies may be required in order to improve response rates and survival in these malignancies.

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