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Myeloprotective Effect of Medroxyprogesterone Acetate (MPA)

Paolo Pedrazzoli

IN A RECENT paper published in *The European Journal of Cancer* Amadori *et al.* [1] evaluate the myeloprotective effect of medroxyprogesterone acetate (MPA) by looking at bone marrow granulocyte–macrophage progenitor cell (CFU-GM) growth in patients with head and neck cancer receiving chemotherapy alone or in combination with the progestin. They conclude that "the myeloprotective effect of MPA is due to its capability to induce mitotic rest in the stem cells which are thus protected from the action of chemotherapeutic drugs", but what they state is not clearly supported by data presented.

Their conclusion relies mainly on results comparing the number of progenitors before and after 2 weeks of MPA treatment; a reduction in CFU-GM growth was observed at day 14 in 7 out of 10 cases. Despite the fact that no statistical significance is reached, they do not give an explanation on the 3 cases in which the number of progenitors increases on day 14. In addition, their conclusion is not supported by any cell cycle analysis.

Further support for a protective role of MPA on bone marrow progenitors comes, in this study, from results comparing CFU-GM growth before and 14 days after chemotherapy. In 8 out of 10 cases of the MPA-treated group an increase of CFU-GM was observed on day 14, while in chemotherapy-alone group there was a reduction of CFU-GM at the same time. However, the authors did not point out and discuss that before chemotherapy the number of progenitors was significantly lower in MPA-treated patients and it was very close in the two groups—101.3 (6.0–187.2) vs. 95.0 (36.7–178.5)—on day 14.

As far as clinical results are concerned, they report 3 cases of grade 1 leukopenia and thrombocytopenia in MPA-treated patients as compared to 4 cases of grade 1 leukopenia and 3 cases of grade 2–3 thrombocytopenia in chemotherapy-alone group. This is, in my opinion, too little to state that "we observed lower haematological toxicity in the peripheral blood stream in arm B" (MPA). Furthermore they did not specify whether the two groups were matched for age, sex, previous myelotoxic therapy, etc.

Our and other experiences [2, 3] have failed to demonstrate a direct *in vitro* effect of MPA on bone marrow progenitor cells. Amadori *et al.* [1] have used a different and interesting approach to study this issue, but their data are not sufficient to draw any conclusions.

In the era of haemopoietic growth factors, the use of MPA to reduce chemotherapy-related myelotoxicity seems unrealistic, although the drug clearly remains an important tool in other oncological settings.

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Myeloprotective Effect of Medroxyprogesterone Acetate (MPA)

D. Amadori

PEDRAZZOLI'S CRITICISM of our paper [1] stems from the statement that the authors' conclusions "rely mainly on results comparing the number of progenitors before and after 2 weeks of medroxyprogesterone acetate (MPA) treatment".

Our conclusions were, on the contrary, based on the comparison of the behaviour of bone marrow activity in each subject, evaluated by counting the colony forming unit granulocyte–macrophage (CFU-GM) before and after a cycle of chemotherapy (CT), in patients treated with MPA (arm B) and in those not treated with MPA (arm A).

Pedrazzoli's main criticism is based on the observation that "before chemotherapy the number of progenitors was significantly lower in MPA-treated patients and it was very close in the two groups −101.3 (6.0–187.2) vs. 95.0 (36.7–178.5) — on day 14". We cannot accept this criticism for the following reasons:

(a) The two randomised groups are comparable in terms of absolute number of CFU-GM before each treatment (day 0 in cases not treated with MPA and day −14 in those treated with MPA). The number of progenitors in the two groups was not, in fact, statistically different at that time

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(153.4 ± 14.17 in arm A, 111.9 ± 15.0 in arm B, P = not significant). It follows that, before treatment, groups A and B of the study in question were equivalent in terms of CFU-GM count.

A comparison between the two 0 days in terms of absolute values of CFU-GM is, therefore, inappropriate because at that time the comparison would be between an MPA-treated group (arm B) and a non-MPA-treated group (arm A).

(b) Our hypothesis of a "protective" bone marrow effect of MPA is based on the analysis of the variance for paired data [1] which shows a significantly different behaviour between the values of CFU-GM observed at time 0 and 14 in MPA-treated and non-treated patients within the two groups.

This analysis does not compare the absolute average value of CFU-GM at time 14, as this data is not representative of the phenomenon studied, but the behaviour in time of bone marrow activity in MPA-treated and non-treated cases. This was significantly different in the two groups and this seems to support the hypothesis of a myeloprotective effect of the drug at the nadir of CT.

Long-term bone marrow rescue, on the other hand, evaluated on the 30th day from the beginning of the last of the three CT cycles, was not affected by treatment with MPA (see analysis).

With regard to the explanation for the increase on day 14 of the number of progenitors in 3 cases, we think that the reasons for this could be problems relating to the absorption or metabolic pathway of the drug in the stem cells.

We agree with the criticism regarding the value of our clinical data, supporting a lower haematological toxicity based on a few cases in whom lower degrees of toxicity were observed.

The data concerning low haematological toxicity observed by us in MPA-treated cases requires further study on larger populations, as we suggested.

As far as the role of MPA as a myeloprotective agent is concerned, in the era of haemopoietic growth factors, we believe that the drug is not an alternative to growth factors, but a complement to them. If our data are confirmed, MPA could be used before and during chemotherapy, while haemopoietic growth factors such as granulocyte colony-stimulating factor or GM-colony-stimulating factor could be employed shortly before the nadir of chemotherapy. In this setting, we would expect that, working on a bone marrow reserve "protected" from chemotherapy by MPA, a better effect of growth factors could be observed and thus perhaps lower doses could be used.

1. Amadori D, Frassineti GL, Flamini E, *et al.* Clinical and laboratory evaluation of the myeloprotective effect of medroxyprogesterone acetate in head and neck cancer. *Eur J Cancer* 1992, **28A**, 1331–1334.

Correction

Role of Interleukin-2 in Regulating Lymphocyte Activation and Recirculation by C. Fortis *et al.* In this article published in Vol. 29A, No. 3, pp. 474–475, Fig. 1 was incorrect. The correct version of Fig. 1 is reproduced below:

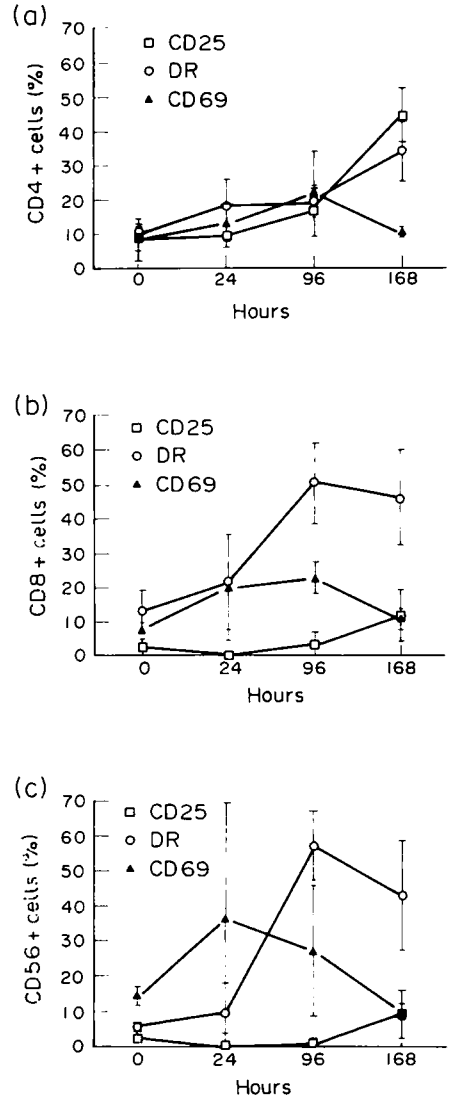

Fig. 1. Percentage of circulating (a) CD4+, (b) CD8+ and (c) CD56+ cells bearing surface activation markers during a cycle of rIL-2 administration.