

## ATRA administration in the critically ill patient

All-*trans* retinoic acid (ATRA) is now widely used as induction therapy for acute promyelocytic leukaemia. Recently, we needed to give ATRA via a naso-gastric (NG) tube, and could find no information about such administration in the literature. We report successful administration when the liquid was mixed with soya oil.

A 12-year-old boy presented with melaena, anaemia and gum bleeding. He was confused, oxygen-dependent and CXR showed an infiltrate. The blood count showed a WBC of  $49 \times 10^9/l$  with 64% blasts. Marrow morphology was typical of AML M3 and marrow cytogenetics demonstrated t(15;17). The patient's high WBC and respiratory status made initial therapy with ATRA inappropriate until the leukaemia burden was reduced. He therefore commenced induction chemotherapy with idarubicin, cytosine and thioguanine. His respiratory status deteriorated, and he required ventilation 24 h later. Therapy with ATRA (Roche Pty Ltd, Sydney, Australia) was initiated 48 h after chemotherapy, when his WBC was  $6 \times 10^9/l$ , at a dose of 40 mg ( $25 \text{ mg/m}^2$ ) daily. The patient was muscle-relaxed with a NG tube in place. Attempts to aspirate the ATRA from the capsules was hampered by it sticking to both plastic or glass syringes. Flushing the viscous fluid with saline or water was also unsuccessful. The parent drug company had no information on use of ATRA via an NG tube, and no parenteral preparation is available. However, the reason that the solution is so viscous is that the ATRA is emulsified in soya oil.

Our solution to this problem was as follows. The capsules of ATRA were cut open and the contents aspirated via a 19-gauge needle into a syringe which had been primed with 1 ml of soya bean oil. After aspiration, on visual inspection, the

capsule retained about half of the original volume of the drug. Small amounts of soya bean oil were mixed with the capsule contents. The resulting reduction in viscosity of the capsule contents allowed more of the ATRA to be drawn up into a syringe. The remaining liquid was flushed out with fresh soya-bean oil. The resulting mixture of ATRA and soyabean oil was stirred to ensure uniformity, placed in a glass syringe and administered via the NG tube within 24 h of preparation.

After 14 days of ATRA administration, plasma levels were measured using a modified version of the method of Smith and colleagues.<sup>1</sup> Levels of ATRA rose from 1.4 to  $2.2 \mu\text{M}$  after the dose. Such high levels and only a minimal increase in response to the additional dose suggest saturation pharmacokinetics similar to the day 28 disposition of ATRA previously reported.<sup>1</sup>

As patients diagnosed with M3 AML frequently have problems with bleeding and infection, we were surprised to find no information on naso-gastric administration of ATRA. As it took several days to acquire the information that allowed us to find a solution for the final method of ATRA administration, we hope this information may be of use to other clinicians who find themselves in the same situation.

PJ SHAW<sup>1</sup>,  
MC ATKINS<sup>2</sup>,  
CE NATH<sup>3</sup>  
and JW EARL<sup>3</sup>

Departments of <sup>1</sup>Oncology,  
<sup>2</sup>Pharmacy and <sup>3</sup>Biochemistry,  
The Children's Hospital,  
Pyrmont Bridge Road,  
Camperdown, Sydney,  
NSW 2050, Australia

Correspondence: Dr PJ Shaw  
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## Comment on published paper (Proctor *et al*, this issue pp 1246-1251)

Selection biases play a major role in the evaluation of bone marrow transplantation. It is generally assumed that more favorable subgroups of patients are subjected to allogeneic BMT. Patients in poor clinical condition or patients who relapse early are usually excluded from this procedure. Only prospective randomized studies or population-based studies are suitable approaches to evaluate the impact of allogeneic BMT on survival. Even prospective randomized studies suffer from selection bias throughout the treatment protocol. For instance in the recently published EORTC/EBMT AML 8a study<sup>1</sup> HLA typing was only performed in 80% of the patients. Out of the 230 patients in complete remission with a histocompatible

sibling donor 168 patients were proposed for allografting and only 144 patients received the allograft. An intention-to-treat analysis resolved this selection bias partly, but the full impact of allogeneic BMT could not be assessed because not all patients were HLA-typed and not all patients were assigned to allogeneic BMT.

For that reason the population-based study of Proctor *et al*<sup>2</sup> (this issue) is very interesting and deserves attention. A strikingly high proportion of patients had a donor (78%) for which no good explanation can be given except for chance. In the age group 15 to 40-years-old, 28 patients had a donor. Three patients were excluded from the intention-to-treat analysis, because of refusal (two patients) or preference for autologous BMT (one patient). These patients should have been included in the intention-to-treat analysis. Nevertheless, the event-free

Correspondence: Prof T De Witte

survival of the remaining 25 patients with a histocompatible sibling donor was significantly better than the EFS of patients of the same age who received chemotherapy alone.

This study shows that population-based studies are very important and useful. We should congratulate Dr Proctor and his co-workers for their efforts and stimulate others to pursue analyses based on the same principles.

T DE WITTE

Department of Internal Medicine,  
Division of Hematology,  
University Hospital Nijmegen,  
Geert Grooteplein 8, PO Box 9010,  
6500 zHB Nijmegen, The Netherlands

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- 2 Proctor SJ *et al* on behalf of the Northern Regional Haematology Group. Evaluation of the impact of allogeneic transplant in first remission on an unselected population of patients with acute myeloid leukaemia aged 15–55 years. *Leukemia* 1995; **9**: 1246–1251.

## Hematopoietic growth factors in drug-induced agranulocytosis

Sprikkelman *et al*<sup>1</sup> published in your columns an extensive review on the therapeutic benefit from growth factors in patients with drug-induced agranulocytosis. We feel that the evidence presented does not substantiate the conclusion that 'G-CSF and GM-CSF enhance the recovery of the myeloid lineage, resulting in a faster normalization of the peripheral blood granulocyte count and a reduced incidence of fatal complications'. Comparing the duration of agranulocytosis in patients treated or not treated with growth factors on the basis of the available literature is misleading: most patients given growth factors were reported as 'case reports' (60 patients were collected from 31 references), while the data on patients not being given growth factors result from population-based studies, encompassing all patients with drug-induced agranulocytosis observed in a given period of time. In the former case, a bias towards reporting patients with a favorable outcome can be reasonably suspected; most investigators would refrain from reporting patients given growth factors and recovering in a not unexpected period of time. Moreover, the editorial policy of some journals but not *Leukemia* favors the publication of optimistic case reports: our first paper reporting a prompt recovery in a patient treated with GM-CSF was immediately accepted for publication;<sup>2</sup> when, after treating three additional patients with less success, we submitted a 'word of caution' to the same editor, it was rejected and finally published elsewhere . . . .<sup>3</sup>

More basically, if, as underlined by Sprikkelman *et al*, most cases of agranulocytosis are antibody-mediated, growth factors are unlikely to be of great help as long as the offending antibody is present. At best, growth factors could contribute to neutrophil recovery relatively late during the course of agranulocytosis, when the offending antibody or drug-anti-

body complex has been cleared. To some extent, this view is supported by Tamai *et al*<sup>4</sup> who conclude that G-CSF hastens recovery in patients already on their way to recovery.

In conclusion, we feel that the efficacy of growth factors in drug-induced agranulocytosis has not been convincingly demonstrated. Treating agranulocytosis with growth factors on a routine basis is premature, especially as severe adverse reactions may result from their use.<sup>5</sup>

A DELANNOY  
and C RAVOET

Hôpital de Jolimont,  
Hematology Department,  
7100 Haine-Saint-Paul,  
Belgium

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## Note from the editor

Policy underlying acceptance of papers is complex. As far as *Leukemia* is concerned, we relish debates and provided statements are circumstantiated by facts – our major criterion – contradictory data are always published.