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SHORT REPORT

Tandem high-dose therapy (HDT) for multiple myeloma: recombinant human erythropoietin therapy given between first and second HDT allows second peripheral blood stem cell transplantation without red blood cell transfusion

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Summary. We evaluated the ability of recombinant human erythropoietin (rHuEpo) therapy, given before high-dose therapy (HDT), to allow autologous peripheral blood stem cell transplantation (PBSCT) without red blood cell (RBC) transfusions. Eleven multiple myeloma patients underwent tandem HDT and autologous PBSC, receiving 500 U/kg/week rHuEpo from d 30 after initial transplant. Haemoglobin levels were 9·5 ± 1·1 g/dl and 12·5 ± 0·9 g/dl at the first and second transplant respectively ($P < 0·001$). RBC transfusions were required for 10/11 patients for the first transplant versus 1/11 for the second ($P < 0·001$). To conclude, a short course of rHuEpo therapy before HDT facilitates the performance of an autologous transplant without RBC transfusions.

Keywords: autologous stem cell transplantation, tandem transplantation, myeloma, erythropoietin, recombinant erythropoietin.

Conventional red blood cell (RBC) transfusions are still associated with a low risk of a number of serious complications (Goodnough *et al*, 1999). It is now well established that recombinant human erythropoietin (rHuEpo) treatment raises haemoglobin (Hb) levels, reduces the need for transfusions and improves quality of life in cancer-associated anaemia (Beguin, 2002). After haematopoietic stem cell transplantation (HSCT), several trials have administered very high doses of intravenous (i.v.) rHuEpo starting on d 1 and continuing for either 1–2 months or until erythroid engraftment. These trials have uniformly shown little (in allogeneic HSCT) or no (in autologous HSCT) clinical benefit (Link *et al*, 1994), with no reduction in transfusion needs observed. On the other hand, we have shown recently that rHuEpo was very efficient when started at least 1 month after an allogeneic transplant, at a time when erythropoietic marrow recovery is accomplished and endogenous erythropoietin (Epo) production is inappropriately low for the degree of anaemia (Baron *et al*, 2002a; Baron & Beguin, 2003). However, this approach would not impact on transfusion requirements when they are most prominent, i.e. in the first month after transplantation.

Tandem autologous HSCT in first-line therapy has been shown to be an optimal treatment option for multiple myeloma (Attal *et al*, 2002). The aim of this study was to investigate whether rHuEpo treatment starting 30 d after the first transplant could increase Hb levels sufficiently to abrogate the need for RBC transfusion after the second HSCT.

PATIENTS AND METHODS

We developed a protocol of rHuEpo therapy in multiple myeloma patients in first-line treatment undergoing tandem autologous peripheral blood stem cell transplantation (PBSCT), with the aim of avoiding RBC transfusions in the second HSCT procedure. RhuEpo was not given before the first transplant, so that patients served as their own internal controls. Eleven patients, five males and six females, aged 44–64 (median 58) years, were included. The collection and infusion of PBSC was carried out as described previously (Andre *et al*, 2003). The percentage of bone marrow plasmocytes was 2 ± 4% and 1 ± 1% before the first and second transplants respectively. Before the first transplant, polymorphonuclear leucocytes (PMN) and platelet counts were 2·79 ± 1·35 and 271 ± 144 × 10^9/l respectively. The

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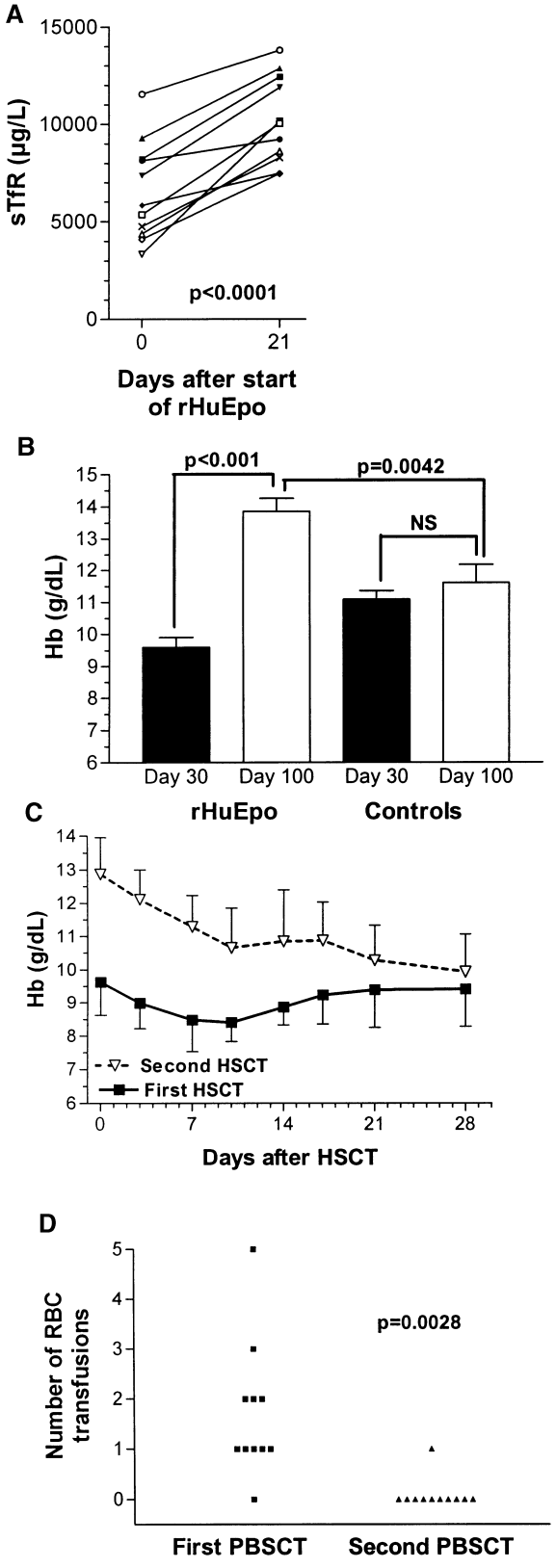

Fig 1. (A) Change in sTfR between d 0 and d 21 after the start of rHuEpo therapy. (B) Hb level on d 30 and 100 after PBSCT in patients treated with rHuEpo ($n = 11$) or in historical controls ($n = 11$). NS, not significant. (C) Hb evolution after the two PBSCT procedures. (D) RBC transfusions in the two PBSCT procedures.

conditioning regimen was 200 mg/m^2 melphalan for both transplants. Patients received a mean of 13·8 ± 10·3 and 15·5 ± 10·3 CD34$^+$ cells/kg as first and second transplant, respectively, representing a non-significant difference, and were treated with granulocyte colony-stimulating factor (G-CSF) after transplantation. Single-donor platelet transfusions were given if platelet counts decreased below 15×10^9/l. The trigger for RBC transfusions was an Hb level of 8 g/dl or below.

Patients were scheduled to start subcutaneous (s.c.) rHuEpo on d 30 ± 3 after the first PBSCT at a dose of 500 U/kg/week (standard dose for cancer anaemia) with the aim of achieving Hb levels of 13 g/dl. Once that target was achieved, the dose was reduced, in order to use the lowest dose capable of maintaining the Hb between 12 and 14 g/dl. As the second HSCT procedure was performed 112 ± 18 d after the first, patients were treated for an average of 12 weeks. Patients with functional iron deficiency (defined by transferrin saturation < 20%) received i.v. saccharose-iron (Venofer®) at a dose of 200 mg/week for 3 weeks.

Complete blood counts, reticulocytes, serum soluble transferrin receptor (sTfR) (a quantitative measure of total erythropoietic activity) (R'Zik & Beguin, 2001), serum Epo and the observed-to-predicted (O/P) ratio were measured as reported previously (Baron *et al*, 2002a,b; Beguin *et al*, 1993).

Unpaired and paired Student's *t*-tests were used to compare biological variables in two groups or to compare baseline values with later measurements in the same group of patients. Welsh's correction was used in cases of unequal variance. The number of patients requiring transfusions was compared using Fisher's exact test.

RESULTS

Efficacy of rHuEpo therapy after the first transplant

The O/P Epo ratio was 0·85 ± 0·11 on d 30 after the first PBSCT, showing relative endogenous Epo deficiency. RhuEpo therapy was started on d 31 ± 4. Erythropoiesis, as assessed by sTfR, increased very quickly from 6577 ± 2539 µg/l at baseline to 10 206 ± 2233 µg/l ($P < 0·0001$) 3 weeks later (Fig 1A). Reticulocytes increased from 66·2 ± 25·7 × 10^9/l to 107·7 ± 50·1 × 10^9/l during the same period ($P = 0·007$). The median time to an Hb increment ≥ 2 g/dl was 4 weeks, and eight out of 11 patients achieved an Hb of 13 g/dl after a median of 8 weeks. The Hb level increased from 9·6 ± 1·0 g/dl at baseline to 13·9 ± 1·4 g/dl on d 100 ($P < 0·001$). There was no correlation with the CD34$^+$ cell dose received. In

comparison, in an historical group of 11 transplanted myeloma patients, Hb increased from 11·1 ± 0·9 to 11·6 ± 1·9 g/dl in the same interval ($P = 0·0042$ for comparison with d 100 Hb in rHuEpo-treated recipients) (Fig 1B).

Comparison of the two transplant procedures

The Hb level was 9·5 ± 1·1 g/dl at first transplant versus 12·5 ± 0·9 g/dl at second transplant. Hb values after the second transplant remained higher throughout the first 2 weeks but reached identical levels on d 28 (Fig 1C). In both transplants, erythropoietic activity decreased after the conditioning regimen, but recovered progressively after d 7. These findings demonstrate that Hb differences between the two PBSCT only resulted from higher Hb values achieved before PBSCT, and not increased erythropoiesis after the second PBSCT.

Transfusion needs

Ten out of 11 patients required RBC transfusions for the first PBSCT, versus one out of 11 for the second transplant ($P < 0·001$) (Fig 1D). RBC and platelet requirements were 1·7 ± 1·3 and 1·0 ± 1·1 for the first procedure versus 0·1 ± 0·3 ($P = 0·003$) and 0·5 ± 0·7 (NS) for the second procedure respectively.

DISCUSSION

Our data demonstrate first the remarkable efficacy of rHuEpo therapy when started 30 d after an autologous HSCT, when endogenous Epo production becomes inappropriately low for the degree of anaemia (Beguin *et al*, 1998), achieving a normal Hb level on d 100, just before the second transplant. In addition, our data demonstrate that the higher Hb levels obtained by rHuEpo therapy after the first transplant permitted the carrying out of the second HSCT procedure without RBC transfusions in > 90% of the patients. Ponchio *et al* (2000) have reported previously, in 10 breast cancer patients, that RBC transfusion requirements can be decreased by rHuEpo therapy started after PBSC collection. However, in that study, patients were compared with historical controls, whereas in our study, patients served as their own internal controls, receiving exactly the same treatment schedule with or without rHuEpo before autologous transplantation. In addition, whereas it was already known that cancer patients on chemotherapy could respond to rHuEpo, we show here for the first time that rHuEpo is at least as efficient when given shortly after recovery from first autologous HSCT.

In conclusion, in tandem autologous PBSCT for multiple myeloma, rHuEpo therapy started 30 d after the first PBSCT permitted performance of the second PBSCT without RBC transfusion.

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