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Editorial

Recombinant Human Erythropoietin (rhEPO) as an Adjuvant for Autologous Blood Transfusion

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RECOMBINANT HUMAN erythropoietin (rhEPO) became available for clinical trials in 1985 and was introduced into clinical practice for treatment of anaemia due to renal failure in 1989. More than 300 000 renal patients throughout the world are now receiving rhEPO. For several reasons this use can be currently considered the gold standard of EPO-therapy. The commonly used weekly maintenance dose of less than 100 IU/kg body weight is cost-effective compared with a regular transfusion requirement of 2–3 units of blood per month. Several clinical studies in the last few years have shown that rhEPO can also be remarkably effective outside nephrology [1]. In the United States, rhEPO is approved for treatment of anaemia induced by zidovudine (AZT) therapy in HIV-infected patients, of anaemia induced by chemotherapy of non-myeloid malignancies and for the reduction of allogeneic blood transfusion in elective surgery patients (with the exception of cardiac and vascular surgery). In some European countries, rhEPO is now approved for potentiation of pre-operative autologous blood donation [2].

Allogeneic blood transfusion came under considerable pressure when information on increased incidence of post-operative infection [3] and possible adverse effects on the prognosis in cancer surgery [4] became available.

Most surgeons now adhere to several techniques to avoid perioperative blood loss, including pre-operative haemodilution, meticulous preparation techniques, cell saving techniques and autologous blood donation. Even if the costs for producing autologous blood units might be twice or even three times the price of an allogeneic blood unit, these costs fairly outweigh the risk and subsequent costs of increased surgical infections or HIV, HBV or HCV inocculation [5]. Therefore, autologous blood donation became widely accepted for patients undergoing hip replacement or spinal surgery where timing of pre-operative autologous blood donation and operation was easily feasible.

Goodnough and coworkers were the first to show that the administration of rhEPO increases the amount of autologous blood that can be collected before surgery [6]. In a randomised, controlled trial of erythropoietin in 47 adults scheduled for elective orthopaedic procedures, the patients received either erythropoietin (600 U/kg body weight) or placebo intravenously twice a week for 21 days, during which time up to 6 units of blood was collected. The mean red-cell volume donated by the patients who received erythropoietin was 41% greater than that donated by the patients who received placebo (961 versus 683 ml, $P < 0.05$).

This study and subsequent clinical trials in patients undergoing orthopaedic surgery demonstrated that for patients who were not anaemic (haematocrit > 39%) at the time of the first donation, erythropoietin therapy had no clinical benefit defined as reduced exposure to allogeneic blood in the setting of aggressive autologous blood donation [2]. Thus, for patients without anaemia, the donation of autologous blood alone remains the standard of care for those who can tolerate aggressive phlebotomy and stimulate sufficient erythropoiesis through their endogenous erythropoietin response [7].

However, patients with gastrointestinal cancer often present with anaemia and depleted iron storage, they cannot tolerate aggressive phlebotomy for autologous blood donation and often require immediate surgical treatment for stenosis. In this issue, Rau and associates (pp. 992–998) [8] report a randomised, placebo-controlled trial examining whether the subcutaneous (s.c.) administration of rhEPO increases the donated red cell blood volume in patients with rectal cancer.

The authors are to be congratulated for a well-designed, randomised double-blind trial in which they were able to show that 200 U/kg body weight rhEPO daily s.c. for 11 consecutive days in non-anaemic rectal cancer patients (Hb level > 12.5 g/dl in males/ > 12 g/dl in females) resulted in a 29% higher mean cumulative volume of red cells donated pre-operatively compared with placebo (571 ml versus 444 ml, $P = 0.02$). The fall in the mean haematocrit from baseline to the last pre-operative value was significantly lower in the rhEPO group (41.4 to 37.6% versus 41.8 to 34.8%, $P = 0.0004$). So they were able to increase the ability of cancer patients to donate autologous blood during an acceptably short pre-operative period and to enhance the restoration of haematological values after the donation period.

What were the clinical consequences?

82 units of autologous blood were harvested in the rhEPO group and 55 in the placebo group, among these, 53 (65%) in

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the rhEPO group and 43 (78%) in the placebo group respectively were given to the patients resulting in a rather low waste rate of 30% overall, 35% in the rhEPO group and 22% in the placebo group. Of all blood units given to the patients, 9 out of 62 (14.5%) were allogeneic in the rhEPO group and 33 out of 76 (43.4%) in the placebo group. Concerning patients, 85.2% in the rhEPO group received autologous transfusions and 18.5% received allogeneic blood, whilst in the placebo group the figures were 82.6% and 39.1%, but this difference was not statistically significant ($P = 0.13$).

Although assessment of blood loss and the ability of autologous blood transfusion was not the principal aim of this trial, there seems to be a moderate advantage in the rhEPO group for the lower rate of allogeneic blood needed, but this may partly be due to the fact that rhEPO group patients lost 1,411 ± 1,093 ml of blood compared with 2,064 ± 1,574 ml in the placebo group, requiring 62 blood transfusions in the rhEPO group and 76 in the placebo group. There is so far, no explanation for the higher blood loss and the higher transfusion rate in the placebo group with the exception that only 1 patient in this group needed eight additional allogeneic blood transfusions. In future studies it might be of interest to analyse coagulation disorders in such a trial.

With autologous blood donation with or without erythropoietin therapy many questions are still unanswered. In modern rectal cancer surgery, there is an increasing number of patients who do not need blood transfusions at all, thereby increasing the waste rate and reducing the cost effectiveness. In our own SAKK (Swiss Group for Clinical Cancer Research) experience, including several hundred rectal cancer patients, the rate of transfused patients came down from 90% in the 1980s to 58.6% in the 1990s [9]. For those who really need transfusions there might not be enough autologous blood units available.

From several studies it is known that patients with baseline haemoglobin levels ranging from 10 to 13 g/dl have the highest risk of requiring allogeneic transfusions and appear to achieve the greatest benefit from erythropoietin therapy [2, 10]. However, using erythropoietin alone in anaemic patients undergoing right hemicolectomy for carcinoma, in very high-doses up to 20 000 units per day for at least 10 days, it is not possible to reduce the need for intra-operative and postoperative transfusion, as has been shown by the authors in another randomised trial [11]. This negative result might be due to the short treatment interval and to iron deficiency. There is general agreement that iron supplementation is important in autologous blood donation programmes with or without erythropoietin therapy. The optimal dose and schedule is far from being known and the same is true for erythropoietin therapy.

Subcutaneous administration is more cost effective than intravenous administration and weekly doses of erythropoietin are more cost effective than daily administration [2]. Subcutaneous injections can be applied by the patients themselves, and the authors have shown that, even in a short period of 11 days, a mean harvest of 3.0 ± 0.8 units of autologous blood in non-anaemic patients is possible, which might be of interest in other cancer surgery areas (e.g. sarcoma) and where treatment-induced anaemia might cause delay in planned surgery.

Autologous blood donation in cancer patients may have a positive impact on immunological function compared with allogeneic blood, but retransfusion of circulating cancer cells may still be a matter of debate. Modern PCR-techniques could be useful in answering this question.

The most conflicting results in the very interesting paper by Rau and colleagues [8] are the data on adverse events. The authors very meticulously listed all adverse events observed during the treatment period, resulting in at least one such episode in 57.1% pre- and 74.1% postoperatively in the rhEPO group and 38.5 and 56.5%, respectively, in the placebo group. More intriguing are the serious adverse events, defined as such by the authors if the event was life threatening, if admission to hospital was necessary or if hospitalisation was prolonged. These serious adverse events occurred nine times in the rhEPO group, mostly in the postoperative period and only twice in the placebo group. Some of the serious adverse events observed in the rhEPO group were related to postsurgical complications, but 1 patient had a complication of the central venous catheter occlusion in the basilic vein and another patient died of pulmonary embolism. All these serious adverse events may not be related to the trial medication (as stated by the authors) but a few may be. Again, coagulation disorder studies should be implemented in further trials [12], as well as optimal dose, schedule and cost effectiveness analysis, before autologous blood donation programmes with or without erythropoietin therapy will become standard care in surgical cancer patients.

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