Epoetin treatment in haematologic malignancy: How to improve response?

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Previous attempts to increase efficacy

The response rate to erythropoietic stimulating agents (ESA) in cancer is around 60%. Improvement has been attempted by using a higher dose of ESA during the first weeks of therapy [1]. Only one study has compared the standard fixed dose versus weight-based dose. In both cases, there is not evidence enough to support these strategies [2].

Selection of patients by baseline s-Epo is another strategy [3,4]. This has been challenged in recent studies [5]. Also, in the individual patient, a cut-off level identified as an optimal predictor for the group has little value. With a s-Epo above 100 U/L, which has often been found to be a negative group response predictor, a considerable percentage of cancer patients still respond to ESA therapy.

In a recent study by Straus et al. [6] 289 patients with LPD were randomised to early (Hb $\leqslant$ 12 g/dl) or late (<9 g/dl) treatment start. The Hb level increased in the 'early' treatment group and decreased in the 'late' group ($P < 0.0001$). More early patients achieved a haematologic response, 70% versus 25%, and had a significantly better QoL gain.

This study gives support for the selection of patients for treatment who start to decline in Hb level early in a series of cytostatic treatments. A recent analysis of the benefit of early anaemia treatment gives further support to this strategy [7].

A new concept: Improved response with addition of IV iron

There are two reasons why addition of iron could be beneficial for response to ESA. First, some patients have small iron stores that will be rapidly exhausted if erythropoiesis is stimulated. Secondly, cancer patients often have functional iron deficiency (FID).

Functional iron deficiency

Inflammatory cytokines induce the expression of the iron distribution regulator hepcidin, down-regulating ferroportin, the exporter of iron from the cells to the plasma compartment [8]. When the release of macrophage iron is decreased, plasma transferrin saturation (Tsat) is lowered, and the erythroblasts in the bone marrow are starved for iron. This disturbance of iron turnover has been named *functional iron deficiency* (FID) and is a major problem in cancer anaemia [9].

FID is characterised by a normal or elevated s-ferritin as a sign of iron repletion and a low Tsat. Further, the percentage of hypochromic red cells in the blood (% HYPO) and the haemoglobin content of reticulocytes (CHr) are reliable indicators of FID [10,11].

In renal anaemia, the concept of FID and its treatment have been well known. Superiority of IV over oral iron supplementation has already been shown, and an ESA-saving effect found, in randomised, controlled studies in the mid 1990s [12,13].

Evidence for improvement of efficacy by adjuvant IV iron in cancer anaemia

In cancer anaemia, the first randomised study showing an increased Hb response with IV iron included 157 patients receiving chemotherapy and rHuEpo 40,000 U per week, comparing the addition of oral or IV iron dextran to no iron [14]. A significant difference in response rates was found, 68% for IV iron versus 36% for oral iron and 25% for no iron ($P < 0.01$). The study has been questioned because of the unusually low response rates in the no-iron and oral-iron groups, which may have been caused by the short treatment duration, 6 weeks, and by the presence of true iron deficiency.

In another randomised, open-label study, IV iron, oral iron and no iron regimens were compared in 187 non-myeloid patients with chemotherapy-related

anaemia treated with rHuEpo 40,000 U/week during 8 weeks [15]. The results showed significant differences between the IV iron group and the other two groups in Hb increase, 2.4 g/dl, 1.6 g/dl and 1.5 g/dl, respectively ($P = 0.0044$ for IV versus no iron), in response rates, 73%, 45% and 41% respectively ($P = 0.029$ for IV versus no iron).

The third and most recent study [16] randomised 67 LPD patients without chemotherapy, with Hb 9–11 g/dl and *proven iron stores*, shown by a positive bone marrow Preussian blue staining, to receive rHuEpo 30,000 U once weekly plus or minus IV iron during16 weeks. There was a significant difference between the IV iron group and the no-iron group with regard to response rate (Hb increase >2 g/dl), 93% versus 53% ($P = 0.001$). The time to response was half as long and the Hb increase was greater (2.91 versus 1.5 g/dl, $P = 0.0001$). Since true iron deficiency was excluded by bone marrow iron staining in this study, the 39% of the whole population with Tsat <20% may be regarded as FID, underlining the importance of this condition in cancer patients. All patients with Tsat <20% in the IV iron group responded with Hb increase >2 g/dl.

Smaller doses of rHUEpo were needed in the IV iron group. At the end of the study, a 25% difference (10,000 U per week) in Epo dose was seen between the arms ($P = 0.051$). The difference translates into a cost reduction of at least €80 per week, depending on local list prices of ESA.

The EORTC guidelines on ESA were published before the last two studies of IV iron supplement in cancer anaemia. Still, the guidelines state that there was grade B evidence to support improved response of ESA with addition of IV iron and that oral iron is ineffective in functional iron deficiency.

Conclusion

In conclusion, the improvement in efficacy of ESA treatment by addition of IV iron has now been convincingly shown both in renal and cancer anaemia, especially in patients with FID.

Conflict of interest statement

None declared.

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