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Editorial Comment

Controversial effect of epoetin in cancer: grounds for a translational research exercise?

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Epoetin, the human recombinant form of erythropoietin, has been available as a pharmaceutical since 1989 for the anaemia of chronic renal failure. More recently, different variants of the drug have also been marketed with an indication for the prevention and treatment of anaemia in patients with solid tumours who are being treated with platinum-based regimens, as well as for other less frequent cancer conditions such as multiple myeloma and non-Hodgkin's lymphoma or chronic lymphocytic leukaemia.

The use of epoetin in patients to treat or prevent anaemia secondary to cancer or resulting from its treatment is based on several clinical trials [1] and two independent systematic reviews have recommended its use in specific clinical conditions. Basically, epoetin is recommended for patients with severe anaemia ($\leqslant 10$ g/l) as an alternative to red blood cell transfusion. In less severe anaemia, the decision to use epoetin should be determined by a careful examination of the clinical circumstances [2,3].

Clinical trials and other non-controlled studies have recently suggested that epoetins may also have a role in the treatment of fatigue, a complex and multifactorial syndrome that is quite frequently associated with cancer and most of the time under-diagnosed [4]. Analyses carried out in well-characterised samples have shown that a low haemoglobin is associated with poor outcome in cancer patients in terms of disease control, quality of life and survival [5,6], and that increasing the haemoglobin by epoetin administration can significantly improve a cancer patient's life [7].

Preclinical biological studies carried out on experimental tumours (breast, ovarian, prostate, and head-and-neck cells) indicate that non-haemopoietic cells also have epoetin receptors and that epoetin might have different and opposite actions on cancer cells, either stimulating their growth and angiogenesis [8–10] or enhancing tumour oxygenation and thus radiosensitivity [11,12]. The latter action was particularly studied in patients undergoing radiotherapy and it was the rationale for the design and conduct of several prospective trials, either controlled or non-controlled [13].

Shasha and colleagues published a prospective evaluation of the effectiveness and safety of once-weekly recombinant erythropoietin (epoetin-α) in 777 anaemic cancer patients with non-myeloid malignancies who were receiving radiation therapy [14]. Among the evaluable patients, treatment with epoetin-α was found to be well tolerated, to increase haemoglobin concentrations, reduce transfusion requirements, and improve functional status and quality of life. In conclusion, the authors comment that 'clinical benefit and the safety profile of epoetin-α in this setting appear to be similar to those observed in anaemic cancer patients receiving chemotherapy'.

These promising results were actually challenged by a very recent randomised clinical trial (RCT). Henke and colleagues [15] randomised 351 patients with anaemia and head-and-neck cancer to receive epoetin-β or placebo (in addition to curative radiotherapy): patients given epoetin-β achieved haemoglobin concentrations significantly higher than in the placebo group, but locoregional progression-free and overall survival were poorer in the epoetin group. These unexpected findings (the trial was actually designed to confirm some preliminary data that suggested epoetin-β could improve cancer control and survival in this specific group of patients through the enhancement of tumour radiosensitivity at high oxygen concentrations) held after

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stratification by tumour status and multivariate analysis controlling for different baseline characteristics.

The discussion that followed the publication is a very nice example of the difficulty of accepting unexpected results, though they have been produced using the best tool we have to test a clinical hypothesis generated by previous studies (i.e. a randomised, double-blind, placebo-controlled trial). Although these results should be considered with caution and confirmed by further studies as recommended by the authors (given that the study was an 'exploratory development trial') and should not be generalised outside of the setting in which they were produced (as promptly pointed out by the pharmaceutical companies marketing the different epoetins) [16,17], a few points should be considered before accepting the hypothesis that the role of epoetin in cancer control/progression is already defined:

1. Biological preclinical studies have identified at least two and opposite actions on cancer cells, one favouring the growth and the other enhancing the cell's sensitivity to treatment.
2. Preliminary clinical studies, mostly uncontrolled or retrospective, suggested the potential role of epoetin in the treatment of cancer patients.
3. Several clinical trials document an effect of epoetins on patient-reported outcomes (fatigue and cancer-specific, quality-of-life measures).
4. The study by Henke and colleagues was disappointing, but actually confirms recently published findings from a breast cancer trial with epoetin. The trial was terminated early as there was an observed increase in the incidence of disease progression in the treatment group compared with placebo group that yielded an observed higher mortality in the epoetin group [18]. In this case also, the unexpected negative results (the trial was designed to confirm previous clinical studies that had shown an association between tumour oxygenation, higher haemoglobin concentrations, and improved survival) were discussed with caution in the light of the potential for an imbalance in risk factors between groups and drawbacks in the trial's conduct.

Although the potential shortcomings of these two clinical trials in head-and-neck and breast cancer patients might impair their findings, limit their interpretation and preclude generalisability, it should be underscored that both studies were randomised experiments specifically designed to confirm uncontrolled preliminary clinical data. Results from these two RCTs challenge the hypothesis that epoetins might improve cancer control and seriously obstruct the clinical significance of the association between haemoglobin concentrations and quality of life.

The existence of underlying biological phenomena cannot be ruled out and further ad hoc studies should be carried out to explain the potential role of biological factors that might modulate the effect of epoetin across clinical subgroups.

The present state of affairs offers a perfect opportunity for translational projects and activities. Translational research is usually defined as the process of translating findings from basic science to the development of a new understanding of disease mechanisms, diagnosis and therapeutics. This definition actually implies a bidirectional process: utilising knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in man and/or determining the biological basis of observations made in individuals. Pharmaceutical companies marketing variants of epoetins worldwide, instead of arguing about the internal and external validity of available evidence from controlled clinical trials, should facilitate and support new preclinical studies to discover the biological basis of the unexpected clinical results.

However, while awaiting the results of translational research, the use of epoetin to treat anaemia associated with cancer therapy should be made in the context of available evidence-based guidelines [2,3] and according to the indications granted by Regulatory Agencies. And, as two pieces of evidence are better than none, the use of epoetins, outside of these indications, should be considered only in the context of very well planned and carefully monitored clinical studies that implement strict ethical safeguards for patients.

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