Haematologica
Journal of Hematology
volume 85 – number 5 – May 2000

Haematologica 2000; 85: 449-450

Editorial and Views

The clinical utility of epoetin in cancer patients: a matter of perspective

Patients undergoing chemotherapy for cancer are at risk of developing anemia.[1] Transfusions of allogeneic red blood cells offer a rapid correction of hemoglobin, thus improving quality of life and physical capacity. As a matter of fact, from 21.9% to 68.9% of patients, according to the type of cytotoxic drug, receive on average from 0.55 to 1.34 units of red blood cells per month during 6 courses of a chemotherapy.[2] Allogeneic blood transfusion is not, however, perfectly safe, even though donor selection to exclude high risk individuals, combined with serologic screening test, has dramatically reduced the risk of blood-borne infections. In addition, a critical blood shortage is reported from around the world. Finally, patients are adverse to receiving blood products for the symptomatic management of anemia. Patients and members of the general population living in Toronto stated they would be willing to pay from US $587 to $613 to substitute transfusions with a safe and effective drug during the entire 4 month period of chemotherapy.[3]

Recombinant human erythropoietin (epoetin) is a candidate drug to replace transfusions. Epoetin is well accepted by patients, may be administered at home, has no evident side effects, and has the potential to prevent or ameliorate anemia and to reduce the need for transfusions. This drove physicians to want the drug for their patients. However, administering epoetin to patients with cancer with the aim of preventing anemia is more costly than transfusions. In Italy, the cost of prophylactic use of epoetin for four cycles of chemotherapy at the recommended dose, i.e. 150 U/kg three times a week, was estimated to be $4,400 per patient, while the cost of transfusional support to the same patients was $206.[4] Moreover, epoetin is effective in abolishing transfusional needs in only half of the patients, and a cost-effectiveness analysis which considered all the risks and benefits of the two treatment strategies, resulted in an incremental cost-effectiveness ratio of more than $100,00/quality adjusted life year,[4] i.e. greater than can be considered acceptable to the health care system. In other words, the prophylactic administration of epoetin to cancer patients receiving chemotherapy would require a large health care expenditure for a modest benefit to patients.[3-7] All these issues brought Governmental offices in most Countries with publicly funded heath care not to reimburse for the use of epoetin. According to the society perspective, Authorities decided not to privilege the preferences of single patients but to follow a principle of equity: since any resource competes with another, the most efficient use of resources in respect to all patients' rights shuold be practised.

This example dramatically clarifies a new paradigm of medicine, that is the ethics of health care. Medicine is a complex interaction of knowledge and activities with principles and decision criteria lying in different paradigms. Physicians are asked to be scientifically correct when conducting or interpreting clinical research (the paradigm of science), and to handle patients' specific characteristics and preferences in a unique and tailored way (the "art" of clinical practice). But in the modern age, doctors are also asked to handle community values when the distribution of health care resources is at stake (the paradigm of health care). Doctors need to consider that the amount of resources is limited, and that every action on one patient may rebound on others. Physicians behaving in accordance with the ethics of health care will not waste a very costly technology in a non-cost-effective manner, e.g. epoetin for patients with cancer, since this would reduce the possibility, to give another example, of using epoetin in patients with end stage renal disease or providing by-pass surgery for patients with coronary artery disease (two examples of cost-effective therapies).

Is the debate about cost-effectiveness of epoetin in cancer anemia closed? Certainly not. Physicians must treat 100 patients on chemotherapy with epoetin to reduce the number of transfusions in 11 of them, since the responders are not easily predicted. A comprehensive sensitivity analysis of epoetin cost-effectiveness[4] showed that, for most of the assumptions made, these results were robust. The exceptions concerned two variables, namely the efficacy and the cost of the drug. By better tailoring its use in patients to those with a high probability of response, i.e. improving the prediction of response, or by halving the market cost of the drug, epoetin became cost-effective. Moreover, until more definitive data are available on the magnitude and costs of the increased risk of bacterial infection associated with allogeneic transfusion, the debate about epoetin in cancer anemia should be not prematurely closed. Most of the analyses did not consider avoidance of post-transfusion bacterial infections as one of epoetin's benefits. A recent retrospective cohort study of 9,598 consecutive patients with a hip fracture who underwent surgical repair documented that serious bacterial infection occurred in 4.6% of them, causing a 28.8% mortality in this group. The adjusted risk of serious bacterial infection associated with transfusion was 1.35 (95% CI, 1.10-1.66).[8] Once the burden of allogeneic blood-facilitated infections was considered, autologous blood transfusions acquired the potential to be cost-effective and even cost-saving, despite previous estimates of very high cost-effectiveness ratios.[9] Translating these considerations to cancer anemia, allogeneic blood sparing by epoetin would consistently reverse toward a cost-effective use of resources if evi-

dence of a higher risk of infection due to allogeneic transfusion becomes strong.[10]

Cost-effectiveness analysis is not only a way to discipline the use of new technologies, but is also a way to acquire new medical knowledge. Epoetin for cancer anemia provides an example of both these uses.

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Gene therapy for X-linked chronic granulomatous disease

Patients with X-linked chronic granulomatous disease (CGD) associated with a defect in Gp91-phox suffer from a severe disease and exhibit the greatest morbidity and mortality of all CGD patients. In particular, they frequently undergo fungal and bacterial infections, which are mainly localized in subcutaneous tissues and are resistant to treatment. Stem cell transplantation is the only curative therapy available so far.

Gene transfer of Gp91-phox into hematopoietic stem cells and subsequent expression of the gene in mature phagocytes may be an attractive therapeutic alternative. However so far, long term studies have yielded disappointing results, mainly because of low transduction efficiencies.

In this issue, Bellantuono *et al*.[1] examine the possible reasons for low titer amphotropic viral production associated with gene transfer of Gp91-phox into hematopoietic stem cells. These basic studies are crucial for development of therapeutic procedures. A number of studies on gene transfer into hematopoietic stem cells have recently appeared in this journal.[2-5]

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