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Commentary

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There are increasing pressures to use blood 'rationally', i.e. to give the safest, most effective product, in an appropriate dose when there is no reasonable alternative. Clinical governance concerns and increasing difficulty in recruiting adequate numbers of donors should encourage analysis of the rationale behind our current clinical practices. Where the intervention carries a real risk of inducing harm, rather than simply showing no efficacy, then the drive to question and analyse treatment policies is even greater.

As Solheim and Wesenberg point out in this issue, children are very particular transfusion recipients in that

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they are likely to live long enough to express the full range of transfusion-related side-effects including iron overload, infections, haemolytic disease of the newborn in future pregnancies and alloimmunisation which impairs the results of future organ transplants.

Children are generally very tolerant of anaemia, at least in the short-term. They have good cardiac and respiratory reserve and moderate their activity levels in relation to their sense of fatigue, being free of the external demands (family, work-related, societal) which are experienced by adult patients. Those undergoing surgery are generally well nourished and free of chronic disease and will therefore rapidly recover from a haemoglobin (Hb) as low as 50 g/l, perhaps with the addition of iron supplements.

There is a very limited evidence base to guide paediatric transfusion policies. While it is appropriate to minimise unnecessary or avoidable transfusions, we must avoid developing such antipathy to transfusion that patients are at risk of life-threatening complications of anaemia or suffer a significant impairment in quality of life. Solheim and Wesenberg describe the tolerance of extreme haemodilution to 30 g/l with hyperoxic ventilation [1]. It is hard to justify such an approach in countries which have a very safe blood supply—demonstrating that it can be done does not support introducing this approach as a matter of routine although it may occasionally be justified for the management of patients who refuse transfusion.

The risk of human immunodeficiency virus (HIV), hepatitis B, and hepatitis C from transfusion has become extremely small. In the UK, the current risk of a donation being infectious for HIV is less than 1 in 2 million, for hepatitis B is approximately 1/100 000 and for hepatitis C is less than 1/200 000 [2]. The Serious Hazards of Transfusion reporting scheme [3] collates reports of all types of serious adverse events caused by transfusion in the UK. In 1999–2000, 291 serious adverse events (mainly errors) were reported. This represents approximately 1 event per 10 000 blood component units transfused. The majority of these events (77%) resulted in no long-term morbidity.

In contrast, a child with acute lymphoblastic leukaemia has around a 30% chance of dying of their disease, or of the complications of therapy, within 5 years of diagnosis [4]. Childhood cancer patients who have survived for 5 years have a 10.8-fold excess mortality over the subsequent two decades, with the main cause of mortality (67%) being recurrence of the original cancer [5]. Treatment-related cardiac and pulmonary dysfunction are also significant causes of mortality.

These figures do not justify ignoring the risks of transfusion when treating these patients. However, it is an indication that we must not lose sight of the potential benefits of transfusion because of excessive concern about transfusion risks.

Although prevention and management of treatment-related side-effects has improved, patients undergoing treatment for malignancy have an impaired quality of life which can, even in children, become intolerable. Adult cancer patients report fatigue as one of the more disabling side-effects of their illness and treatment [6]. It is a symptom which impairs their ability to deal with other problems—pain, nausea, anorexia—and reduces their tolerance and enjoyment of interactions with family and friends This fatigue is due, at least in part, to a reduced Hb level, even though this reduction may be relatively minor (Hb 90–100 g/l) [7]. Raising the Hb level can be readily achieved by transfusion, but at least 50% of patients with malignancies will also respond well to epoetin alpha with a significant improvement in quality of life [8]. Solheim and Wesenberg suggest a transfusion threshold of 80 g/l in patients with malignancies, but the epoetin alpha studies demonstrated that, in adult patients, raising the Hb from a mean value of 9.2 g/l to around 110–120 g/l was associated with a notable improvement in quality of life [9,10]. The action of epoetin alpha in raising Hb levels is delayed, generally around 2–6 weeks, but it results in more stable Hb levels than can be achieved by transfusion and results in the production of young red cells which have a normal life-span. Unfortunately, cost-benefit analyses of epoetin alpha versus transfusion in the prevention of chemotherapy-induced anaemia do not currently support abandoning transfusion in favour of epoetin alpha. One analysis showed a marginal cost of greater than $100 000 per quality-adjusted life year (QALY) gained [11].

Hypoxia may have a number of effects on tumour growth. Hypoxia generates genetic instability by acting as an inducer of fragile sites [12] and also acts as a selective agent for resistance to apoptosis [13]. In a study of vascular endothelial growth factor (VEGF) levels [14] in patients with a variety of malignancies, higher levels were found in those with Hb concentrations below 130 g/l compared with those with higher Hb levels. In theory, increased VEGF secretion may stimulate angiogenesis and thus tumour growth and dissemination. The potential impact of these changes on the efficacy of chemotherapy has not been determined. Hypoxia also has an impact on tumour responses to irradiation. Following exposure to ionising radiation, highly energised free radical particles generate DNA strand-breaks within the tumour. Hypoxia limits the availability of molecular oxygen which is essential for the production of these free radical species. The combination of hypoxia and radiation sets the scene for the selection and expansion of tumour phenotypes which are tolerant of hypoxia. Haemoglobin levels below 120–135 g/l appear to be associated with tumour hypoxia and poorer outcomes with radiotherapy in a number of patient populations [15]. These studies suggest that the

100 g/l threshold proposed by Solheim and Wesenberg may not, in fact, be high enough. However, it should also be born in mind that the reaction of normal tissues to irradiation may mirror that of tumour cells in hypoxic conditions. In one recent study, mucositis and dermatitis occurred more frequently, and with greater severity, in patients with a Hb >110 g/l, in comparison with those with a Hb <110 g/l [16].

From these observations, admittedly derived mainly from adult patients, it is clear that there are a number of special issues to be considered in the management of anaemia in patients with malignancy. It seems not unreasonable to extrapolate the adult findings to the paediatric patient group. A relatively mild degree of anaemia may have a significant impact on response to radiotherapy in addition to reducing quality of life. It is possible that, overall, the impact on tumour response is as significant an issue as any concerns about transfusion-transmitted infection. This may be difficult to quantify, but is ample justification for revisiting transfusion practices in these young patients.

Platelet therapy raises additional issues. Platelets are the most common cause of septic transfusion reactions and, like fresh frozen plasma (FFP), are significantly more likely than red cells to cause an allergic or anaphylactic reaction [3]. The evidence for thrombocytopenic morbidity and benefits of platelet transfusion in patients with cancer has recently been reviewed by the American Society of Clinical Oncology (ASCO) [17]. The recommended threshold for platelet prophylaxis in stable patients of 10×10^9/l will reduce platelet use by 20–30% in units which currently operate a threshold of 20×10^9/l. There is no evidence that this reduced threshold will increase the incidence of significant haemorrhage. Although Solheim and Wesenberg recommend a threshold of 20×10^9/l for stem cell transplant recipients, the ASCO review suggests that the lower threshold of 10×10^9/l can be applied equally to this group. Patients with necrotic tumours, or with tumours being treated with irradiation (especially bladder tumours), merit separate consideration as these are commonly sites of spontaneous bleeding, even in those with only moderate thrombocytopenia. Administration of tranexamic acid or desmopressin may reduce platelet requirements and the potential role of tranexamic acid as a cancer treatment in its own right gives this approach particular appeal [18]. Finally, in patients with platelet refractoriness or who otherwise appear to have an unmanageable bleeding tendency, recombinant activated factor VII (rFVIIa) may be rapidly effective. This agent represents a major breakthrough in the management of patients with a wide range of coagulation deficiencies [19].

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