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Current Controversies in Cancer

Are Allogeneic Blood Transfusions Acceptable in Elective Surgery in Colorectal Carcinoma?

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SUMMARY AND OUTLINE

It is our point of view that allogeneic blood transfusions are not detrimental to patients undergoing surgery for colorectal cancer. Although blood transfusions may induce some immunosuppression in surgical patients, this is by no means comparable to that which occurs in transplant patients under immunosuppressive treatment. These patients are the 'gold standard' for the transfusion phenomenon, but are very different from surgical (cancer) patients. To believe that, if anything, blood-induced immunosuppression may enhance tumour growth, underestimates the versatility of the immune system and overestimates the immunogenicity of tumours. There may be other, still unknown, reasons why blood transfusions may influence tumour growth. However, the results from three prospective randomised clinical studies do not support the notion that the alternatives for allogeneic blood are beneficial for patients with colorectal cancer.

TRANSFUSION AND IMMUNITY

The statement that blood transfusions are able to modulate the immune capacity of the host is no subject of controversy or discussion. Most of us accept it as scientifically proven that transfusions trigger the immune system in such a way that the ultimate outcome is immunosuppression, especially when more than one transfusion is given. This notion is fuelled by many reports from the field of transplantation, indicating that transfused patients accept their graft better than non-transfused patients [1]. We believe that this notion needs some fine-tuning.

Transplantation patients form a special group of patients and should not be compared to other groups of patients that need to be transfused. If transfusions are given to a patient on dialysis awaiting a kidney graft, the immunological soil for such a transfusion is completely different from that of an average surgical patient. Furthermore, a transplant patient not only receives an additional huge 'transfusion', namely a graft, but also a cocktail of powerful immunosuppressive drugs. Nobody will disagree that a transplant patient will process his transfusions completely different than a common surgical patient. Still, this immunocompromised transplant patient is generally brought up as the example of what transfusions may do to a patient: induce immunosuppression. The mistake that is made is 2-fold. Firstly, although a substantial number of transplant patients respond to a transfusion with immunosuppression, at least 30% react differently and become immunised. Secondly, as already stated, the immune capacity of a transplant patient is not to be compared with the immune status of a surgical patient. To put it bluntly: it is like comparing a patient with AIDS with a patient having the 'flu'. It may be argued that the transplant patient immunologically is relatively normal at the time of transfusion and, therefore, is not too different from a surgical patient. This argument does not hold because it is known that transfused cells can survive for a long time and will be present and processed at the moment of transplantation and immunosuppressive treatment. However, there is a common denominator that is shared by transplant patients and surgical patients, namely surgery. There is experimental evidence that the immune modulation evoked by surgery may facilitate and enhance immunosuppression by blood transfusions [2].

IMMUNOSUPPRESSION AND TUMOUR GROWTH

Let us return to the gold standard of blood-induced immunosuppression: the transplant patient. We know that immunosuppressive therapy significantly increases the incidence of certain malignancies that arise *de novo* after transplantation. Pertinent to the question as to whether immunosuppression by blood transfusions might adversely affect colorectal cancer prognosis, is the question whether

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immunosuppressive therapy affects the course of *pre-existing* tumours. Penn studied the recurrence rates of pre-existing malignancies that occurred in renal transplant recipients [3]. In a group of 78 patients a tumour was diagnosed and/or treated at an average period of 3 months after transplantation. Interestingly, 63% did not develop recurrences during an average follow-up period of 53 months. This figure underlines the negligible influence of the immune system with regard to the progression of existing tumours, even in a situation of marked immunosuppression.

CLINICAL TRIALS

Blood transfusions administered during cancer surgery are given for various reasons which by themselves may influence cancer prognosis. These transfusion-associated variables may function as confounding factors when the relationship between transfusions is studied. In a nutshell, this is the difficulty in establishing the existence of a deleterious effect of blood transfusions. In evaluating the impact of various clinical studies, it is important to realise that the susceptibility for confounding factors is clearly associated with the type of study which is performed. This susceptibility is high in retrospective studies, moderate in prospective observational studies and low in prospectively randomised studies.

Up to now 31 observational and three prospectively randomised, controlled, clinical trials on the effect of blood transfusions on recurrence rate and survival in patients with colorectal cancer have been published. Of the 31 studies, 16 reported a detrimental effect of transfusions and 15 failed to detect any transfusion effect. Recently, Vamvakas performed a meta-analysis on 28 of these observational studies (21 retrospective, seven prospective) [4]. He found that the association of peri-operative transfusion with a negative outcome was significant when all retrospective studies were combined. However, in the case of the prospective studies, the transfusion effect did not attain significance. Of the seven teams of investigators who had conducted the prospective investigations, only one team concluded that transfusions had a deleterious effect. Three prospective, randomised controlled trials have been performed thusfar. In two studies, performed by ourselves [5] and Heiss and colleagues [6], transfusion of predonated autologous blood was compared with allogeneic blood. In the study by Houbiers and associates leucocyte-poor allogeneic blood was compared with leucocyte-depleted allogeneic blood [7].

The results of our own study comprising 475 patients were clear: there was no significant difference in disease-free survival or patient survival rates at 4 years between the two groups. However, we found that the risk of recurrence was increased in transfused patients, either allogeneic or autologous, as compared with patients who had not required a transfusion. Thus, regardless of their type, transfusions appeared to be associated with a poor prognosis, probably because of the (confounding) circumstances that necessitated them.

In the second randomised trial from The Netherlands, Houbiers and associates compared the impact of leucocyte-poor versus leucocyte-free transfusions in 697 patients. No differences were found with regard to survival, disease-free survival or cancer recurrence rates after an average follow-up period of 36 months. Similar to the autologous transfusion trial, non-transfused patients had a longer 3 year survival than patients who had been transfused with blood of any sort.

The third randomised trial was performed by Heiss and colleagues in 120 patients and had a comparable format to the autologous trial mentioned above. After a median follow-up duration of 22 months no significant difference in disease-free survival was noticed. Multivariate analysis showed that the need for allogeneic blood was an independent predictor of tumour recurrence.

The results of these randomised trials indicate that two alternatives for allogeneic blood, namely autologous blood or leucocyte-depleted blood, do not lead to a better prognosis for patients with colorectal cancer. In our opinion this is the only clinically relevant conclusion that can be drawn because it reflects the intention of the trials.

Therefore, we hold the view that allogeneic blood is acceptable for patients with colorectal cancer, simply because the alternatives have been demonstrated to not be beneficial.

1. Opelz G. The role of HLA matching and blood transfusions in the cyclosporine era. Collaborative Transplant Study. *Transplant Proc* 1989, **21**, 609–612.
2. Singh SK, Marquet RL, de Bruin RWF, Hop WC, Westbroek DL, Jeekel J. Consequences of blood loss on growth of artificial metastases. *Br J Surg* 1988, **75**, 377–379.
3. Penn I. The effect of immunosuppression on pre-existing cancers. *Transplantation* 1993, **55**, 742–747.
4. Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. *Transfusion* 1995, **35**, 760–768.
5. Busch ORC, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 1993, **328**, 1372–1376.
6. Heiss MM, Mempel W, Delanoff C, *et al.* Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. *J Clin Oncol* 1994, **9**, 1859–1867.
7. Houbiers JGA, Brand A, van de Watering LMG, *et al.* Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994, **344**, 573–578.

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