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INTRODUCTION

THERE IS no doubt that the introduction of blood transfusions has allowed surgeons to perform successfully even the most delicate operations. However, the risks associated with the use of allogeneic blood are not negligible, and can represent a substantial hazard for exposed patients [1].

In 1981, Gantt hypothesised that the immunosuppressive effect of blood transfusions, largely used in renal transplantation, could also be applicable to cancer patients [2]. The mechanism of this recognised effect in dialysis patients is still obscure and mostly involves a generalised suppression of cell-mediated immunity [3–5]. However, both in normal and in cancer surgery, a specific immunosuppression attributable to transfusions is not always documented and, in a sizeable percentage of cases, even an immune reaction is recorded. However, transfusions are being increasingly associated with postoperative infections, a sign of immune suppression [6–8]. Moreover, it is debatable whether the immunological status of cancer patients can be compared with that of allograft recipients, who differ largely with respect to the type and duration of antigen expression [9].

Many animal studies have been performed with the aim of improving the understanding of the role of blood transfusions on cancer growth, but their results are conflicting due to large differences in timing and route of transfusions, as well as in tumours and species tested [10, 11]. Specifically, these studies have failed to identify the blood component(s) responsible for the immunosuppressive effect: red blood cells, white blood cells, platelets and plasma proteins have all been involved [12, 13].

CLINICAL STUDIES

In the last 17 years many authors have investigated the relationship between the outcome of patients with various cancers and blood transfusions, the greatest amount of research having been conducted on colorectal cancer: our recent meta-analysis has identified 131 papers published up to December 1996, leading to 32 clinical studies analysing colorectal cancer recurrence in over 11 000 patients [14]. These studies were widely differing in their populations (especially in the proportion of patients with rectal cancer), designs (only seven were randomised trials) and type of analysis. However, nearly two-thirds of them reported a significant detrimental effect of transfusions on recurrent tumours and 11 of 19 found transfusions to have an independent effect on recurrence after controlling for possible confounders with multivariate analyses [14]. The pooled estimates from these studies showed a harmful transfusion effect, with overall odds of recurring 68% higher in the transfused patients (odds ratio (OR) 1.68, 95% confidence interval (CI) 1.54–1.83). Stratified analyses confirmed the overall results (Figure 1) and agreed with our initial findings, reported in 1991 [15], and the more recent findings of Chung and colleagues [16] and Vamvakas and Moore [17]. In particular, Vamvakas and Moore computed an effect which was similar to ours when only prospective studies were taken into account and their subsequent meta-analysis 'for explanation' led them to conclude that a possible effect of confounding could not completely explain the unadjusted transfusion effect [18].

Four randomised controlled trials have been performed with the specific aim of verifying the detrimental association between transfused blood and colorectal cancer recurrence. Tartter designed his study to test the effect of allogeneic packed red cells and showed a 2.5 times larger detrimental effect of blood transfusions [19]. Two of the other three studies compared the allegedly less immunogenic autologous blood to allogeneic blood: Heiss and colleagues showed a two times higher risk of recurrence with transfusions, although their 95% CI was not significant [20], and Busch and associates highlighted a detrimental effect of transfusions (OR = 1.85, 95% CI 1.22–2.82), although they attributed the increased transfusion risk to the conditions necessitating the transfusions [21]. Finally, Houbiers and co-workers showed a non-significant effect of allogeneic leucocyte-free blood on recurrence (OR = 1.23, 95% CI 0.87–1.73) but, surprisingly, they did find a difference in survival [22]. The latter studies have raised some methodological questions, especially about the feasibility of effective autologous blood donation programmes, given the high proportion of patients receiving

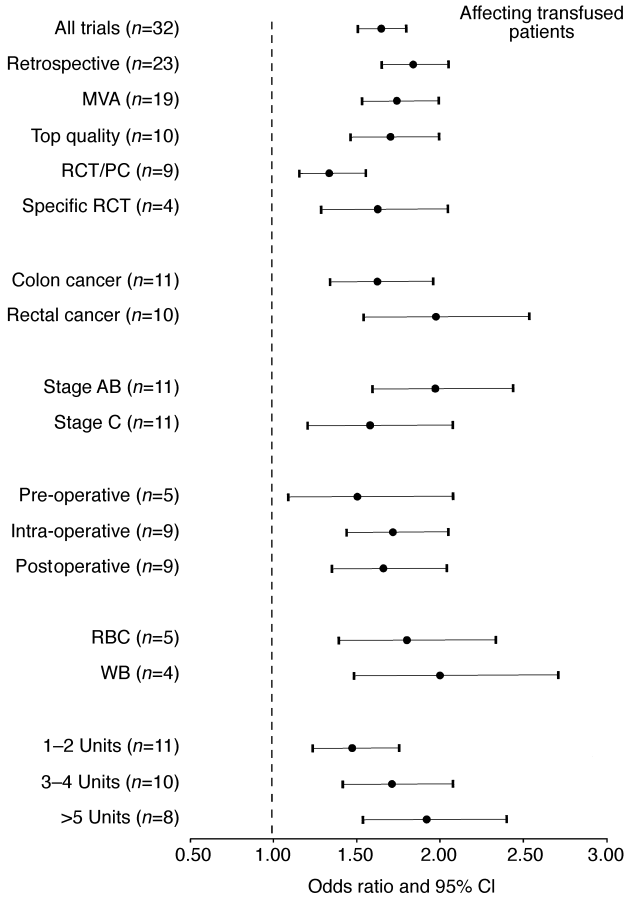

Figure 1. Odds ratios and 95% confidence intervals for the transfusion effect in different patient populations (numbers in parentheses are studies with information). MVA, studies with multivariate analyses; top quality, studies in the upper 25% of the quality score; RCT/PC, randomised controlled studies and prospective cohorts; RBC, studies reporting on the effect of red blood cells only; WB, studies reporting on the effect of whole blood only.

allogeneic blood even in the autologous arm. Interestingly, the pooled effect computed in these randomised studies showed a detrimental association of transfusions to cancer recurrence [14]. Accordingly, a stratification of all the included studies confirmed this detrimental effect separately on rectal and colon cancers and on early and advanced Dukes' stages. Our results also suggested a dose–response relationship and a relative independence of the transfusion effect from their timing and the blood product used.

However, it remains to be verified whether other prognostic factors, that can be independently associated with blood transfusions and cancer recurrence, act as confounders. Variables such as degree of pre-operative anaemia, duration of operations, seniority of surgeons, or surgical technique can help to clarify whether transfusions are causally related to recurrence, or are simply an indicator of poor prognosis tumours which cause severe anaemia necessitating transfusions and are, therefore, at increased recurrence risk *per se* [23, 24].

In my opinion, the data accumulated so far allow the conclusion that there is indeed an association between blood transfusions and increased risk of recurrence in colorectal cancer patients operated for cure. This conclusion should represent the working hypothesis for future large trials, whose huge challenge will be to clarify the causality of this association, whilst also controlling for surgical procedures, quality and type of blood to administer, target haematocrit and use of concomitant drugs [25–32]. However, the feasibility of such trials is not straightforward, given their very likely multicentre nature and the number of factors to control for. An alternative approach could be the development of an international registry capturing the key data of the patients already enrolled in the completed studies, as well as of those to be enrolled in future trials. This would create a comprehensive database which, through an accurate patient-based meta-analysis, could address many of the still unclear issues.

In the meantime, carefully restricted indications for blood transfusions seem warranted in colorectal cancer patients undergoing curative surgery.

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