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THE CUTTING EDGE: RESEARCH UPDATE

Platelet transfusion strategy for hematologic cancers

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Background

In patients with hematologic cancers, severe thrombocytopenia frequently develops as a consequence of the disease or its treatment. Platelet transfusions are usually administered as prophylaxis, to increase low platelet counts, and to reduce the risk of bleeding [1, 2]. It has been shown that the threshold for prophylactic platelet transfusions can be reduced from the previous guideline of 20,000 platelets per cubic millimeter to 10,000 per cubic millimeter without increasing the risk [3]. Furthermore, a recent study [4] suggests that a policy of giving platelet transfusion only as treatment for bleeding can become a suitable choice in low-risk adult patients with hematological cancers, although the primary end point of the study was not a relevant outcome such as the reduction in the number of platelet transfusions. Thus, the effectiveness of prophylactic platelet transfusion to prevent bleeding remains unclear.

Summary

The "Trial of Prophylactic Platelets" (TOPPS) was conducted to assess whether a policy of not giving prophylactic platelet transfusions was as effective and safe as a policy of providing prophylaxis in hematologic cancer patients. [5] The TOPPS was a randomized, open-label, non inferiority trial performed at 14 centers in the United Kingdom and Australia. Patients were randomly assigned to receive, or not to receive, prophylactic platelet transfusions when platelet counts were less than 10×10^9/L [3, 4]. Eligible patients were persons 16 years of age or older who were receiving chemotherapy or undergoing stem cell transplantation, and who had or were expected to have thrombocytopenia (platelet count $<50 \times 10^9$/L) for at least 5 days. The main exclusion criteria were: previous bleeding episode (WHO grade 2, 3 or 4,) inherited hemostatic or thrombotic disorder, requirement for therapeutic doses of anticoagulant agents, diagnosis of acute promyelocytic leukemia, or prior randomization in this trial. The primary end point was bleeding events of WHO grade 2, 3 or 4 up to 30 days after randomization. Secondary outcomes included the number of days with bleeding events; time to first bleeding from randomization, numbers of platelet and red cell transfusions, time until recovery from thrombocytopenia and time in the hospital. The study was designed to have a 90 % power, a one-sided significance level of 5 %, and a non-inferiority margin of 10 %; thus 280 patients were required in each group considering a rate of bleeding events of 20 % in the prophylaxis group. At blinded and prespecified interim analysis after 100 patients, the overall event rate was higher than expected (48 %,) and a greater non-inferiority margin was allowed (15 %.) Statistical analysis was made according to the intention to treat principle.

A total of 600 patients (301 in the no-prophylaxis group and 299 in the prophylaxis one), underwent randomization between 2006 and 2011. Bleeding events of WHO grade 2, 3 or 4 occurred in 151 of 300 patients (50 %,) in the no-prophylaxis group, as compared with 128 of 298 (43 %,) in the prophylaxis group (adjusted difference in proportion, 8.4 percentage points; 90 % confidence interval, 1.7–15.2;

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$P = 0.06$ for non-inferiority), therefore, non-inferiority of no prophylaxis strategy is not shown. In relation to secondary outcomes, the patients in the no-prophylaxis group had more days with bleeding and a shorter time to the first bleeding episode than did patients in the prophylaxis group. Platelet use was markedly reduced in the no-prophylaxis group. The proportion of patients with serious adverse events did not differ significantly between the study groups (6 % of patients in the no-prophylaxis group [18 of 300 patients], and 7 % of those in the prophylaxis group [20 of 298]).

Strengths of the study

- It deals with a clinically relevant problem.
- The compliance with the protocol was good with few patients lost to follow-up.

Weakness of the study

- Bleeding events of WHO grade 2 are heterogeneous, and may be considered to have varying degrees of clinical significance. So, we wonder if the clinically relevant bleedings that are the primary outcomes of the study are well identified by the WHO scale.

Question marks

- The authors increased the non inferiority margin from 10 to 15 % after a prespecified interim analysis showed that the overall frequency of primary outcomes was higher than expected. Considering that the selection of the non-inferiority margin is pivotal in non-inferiority trials, it may be important to understand the choice of increasing the margin to 15 % rather than, for example, modifying the sample size of patients to be recruited.
- Few data on the other bleeding risk factors among patients were provided; it might be useful if other factors (i.e. drugs, acquired von Willebrand disease, refractoriness to platelet transfusion), could help in understanding the high frequency of bleeding events.

Sponsorship

The trial was supported by grants from the National Health Service Blood and Transplant Research and Development Committee and the Australian Red Cross Blood Service.

Clinical bottom line

The use of prophylaxis with platelet transfusion in patients with hematologic cancer and platelet count lower then 10.000/mmc show benefit of such therapy in preventing bleeding as compared with a strategy of no prophylaxis. Further studies may be needed to evaluate whether prophylactic platelet transfusion is necessary in a subgroup of patients such as low-risk adults with hematological cancers (i.e. undergoing autologous stem cell transplantation).

Conflict of interest None.

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