The Gordian knot: ruxolitinib or transplants for high-risk myelofibrosis

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The recent European Bone Marrow Transplant Group/European LeukemiaNet (EBMT/ELN) guidelines for hematopoietic cell transplant in myelofibrosis considered the timing of transplantation in the context of ruxolitinib therapy[1] and recommended: *"Transplant eligible patients who received JAK inhibitors should be carefully and systematically assessed for response [to ruxolitinib] and after six months of therapy, patients falling into the high-risk category of the RR6 model should be evaluated timely for transplant."* The recommendation was based on a model interrogating co-variates correlated with survival after 6 months of ruxolitinib therapy: ruxolitinib dose <20 mg twice daily at baseline, palpable spleen length reduction ≤30%, and red blood cell transfusion frequency.[2]

In this issue of *Haematologica*, Okada *et al*. present a decision analysis Markov model addressing a strategy of ruxolitinib first with transplant when ruxolitinib fails, suggesting this is better than immediate transplantation in people with myelofibrosis who are potential transplant recipients calibrated according to the subjects' age.[3] The authors claim that in subjects <60 years old, there is no difference in terms of quality-adjusted life years (QALY) between the ruxolitinib-first and transplant-first strategies, whereas in older people the ruxolitinib-first option was better.

In considering data obtained using this method of analysis physicians who reason based on the paradigm of evidence-based medicine are challenged by several uncertainties. First, they may wonder how to judge the strength of the evidence derived from the model and whether this evidence applies at the level of patients. In other words, they may ask whether the resulting 0.23 QALY (or 2.8 quality-adjusted months) benefit of ruxolitinib-first in people >60 years old justifies this recommendation.

The analytical Markov model requires a synthesis of relevant literature pertaining to the natural history or risk of a disease, effectiveness and risks of interventions and health-related quality of life. Because differences in the model outputs are not the result of a frequentist statistical framework there is no hazard ratio on which to base the quality of evidence. This is probably the reason why historically, in the hierarchy of evidence, decision models rank lower than evidence from randomized clinical trials.[4] The low-quality evidence from the model was highlighted by the authors: "[C]*onsideration of the risk of chronic graft-versus-host-disease (GvHD) might help when making individual decisions*." This customized decision was derived from results of sensitivity analyses showing the utility of being alive without chronic GvHD strongly influenced the model prediction.

Another critical challenge for followers of evidence-based medicine is whether the clinical question underlying the decision analysis of Okada *et al*. is the most clinically relevant one. Posing the right question is a requirement of evidence-based medicine. In other words, are we sure physicians treating someone with intermediate-2- or high-risk myelofibrosis are always uncertain whether to start with ruxolitinib or a transplant? This is unlikely.

Okada *et al.* chose this analytic decision framework consistent with subject inclusion criteria used in most clinical trials measuring the efficacy of ruxolitinib in myelofibrosis. The US Food and Drug Administration and the European Medicines Agency approvals of ruxolitinib in people with intermediate- and high-risk myelofibrosis represent diverse clinical presentations. There are many articles claiming one or other biomarker can accurately predict leukemia transformation or death, including ≥10% blood or bone marrow blasts, platelet count ≤50x10^9/L and chromosome 17 aberrations.[5] People with *TP53* mutations have poor survival because of high rates of leukemia transformation.[5]

Physicians treating myelofibrosis recognize that choosing the appropriate therapy for these people is challenging. In the absence of data from randomized clinical trials they replace evidence with *clinical judgment*. Some argue if you wait to ascertain a response to ruxolitinib (or potentially

other new drugs) it may be too late to cure someone with a transplant. For example, in one study subjects with *TP53* mutations were less likely to have received pretransplant ruxolitinib compared with the others.[6]

Another limitation of prediction models is they estimate benefits and risks for populations rather than for individuals. Unavoidably, in the model some people in a high-risk cohort have a lower risk of death than others in a low-risk cohort. Moreover, no data from randomized clinical trials prove doing a transplant because of very high-risk disease improves outcomes.

Finally, co-variates correlated with a poor outcome following ruxolitinib treatment are also correlated with a poor outcome after transplantation because they reflect adverse disease biology regardless of therapy.[7] What is needed, but is lacking, is convincing evidence of a differential efficacy of transplantation over ruxolitinib.

A critical question in myelofibrosis is the best pretransplant intervention(s) for "very high risk" people. Does the Okada's Markov model address this? Giving these people ruxolitinib first results in a greater probability of non-response and death compared with the model baseline, guaranteeing a decreased utility of this option. However, there is also evidence of decreased utility of an immediate transplant because of the adverse disease biology of very high-risk people. A threshold analysis would be useful for implementing the decision of which intervention first is better. Given that there are no data addressing this question we conclude that the best decision is to get more data.

A request for more evidence on whether immediate transplant or ruxolitinib first is better in people with very high-risk myelofibrosis is asking for the moon because a randomized controlled trial clashes with patients' and physicians' bias against immediate transplant. We highlighted this problem in deciding whether ruxolitinib improves survival in high-risk people.[8] A solution may be innovative trial designs such as partially randomized individual preference trials which assign potential subjects with a preference to that therapy while randomly assigning those without a preference to alternatives.[9] We hope myelofibrosis researchers will be open to new trial designs in a disease with many unresolved clinical questions.

Disclosures

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