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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 haemopoietic cell transplant in myelofibrosis considered the transplant timing in the context of ruxolitinib therapy. [1] The recommendation: *"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 RBC transfusions frequency. [2]

In this issue of the Journal Okada et al. present a decision analysis Markov model addressing a strategy of ruxolitinib first with transplant decision when ruxolitinib fails is better than immediate transplant in persons with myelofibrosis who are potential transplant recipients and calibrated to subject age. [3] The authors claim that in subjects < 60 years there is no difference in terms of quality adjusted life years (QALYs) between ruxolitinib first and transplant first strategies. In contrast, in older persons the ruxolitinib first option was better.

In considering data obtained using this analytical 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 patient level. In other words, they may ask if the resulting 0.23 QALYs (or 2.8 quality adjusted months) benefit of ruxolitinib first in persons > 60 years justifies this recommendation.

The analytical Markov model requires a synthesis of relevant literature pertaining to the natural history or risk of the 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 compared with evidence from randomized clinical trials (RCTs). [4] The low-quality evidence from the model was highlighted by the authours: [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 asking if 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? Unlikely.

Okada *et al*. chose this analytic decision framework consistent with subject inclusion-criteria used in most clinical trials measuring efficacy of ruxolitinib in myelofibrosis. The US FDA and EMA approvals of ruxolitinib in people with intermediate- and high-risk myelofibrosis represent diverse clinical presentations. There are many articles claiming one or other biomarkers can accurately predict leukaemia transformation or death including blood or bone marrow blasts ≥ 10 percent, platelet concentration ≤ 50 x 10xE+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 choosing the appropriate therapy for these people is challenging. Absent data from RCTs they replace evidence with *clinical judgment*. Some argue if you wait for ascertain 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 withTP53 mutation were less likely to have received pretransplant ruxolitinib compared with others.[6]

Another limitation of prediction models is they estimate population rather than individual benefits and risks. Unavoidably, in the model some persons in a high-risk cohort have a

lower risk of death compared with others in a low-risk cohort. Moreover, no data from RCTs prove doing a transplant because of very high-risk disease improves outcomes. Finally, co-variates correlated with a poor ruxolitinib outcome are also correlated with a poor transplant outcome. because they reflect adverse disease biology regardless of therapy.[7] What is need but absent are convincing data of a differential efficacy of transplants over ruxolitinib.

A critical question in myelofibrosis is the best pretransplant intervention(s) of "very high risk" people. Does the Okada 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 decrease in utility of this option. However, there is also evidence of decreased utility of 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 *best*. Given no data addressing this question we conclude the *best* decision is to get more data.

A proposal to get 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 RCT clashes with patient and physician 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 trials designs in a disease with many unresolved clinical questions.

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