EDITORIAL

Is there consensus on consensus?

We read with interest the typescript by Kröger et al.[1] regarding European Blood and Marrow Transplantation/European Leukemia-Net (EBMT/ELN) consensus recommendations for the use of hematopoietic cell transplants in persons with myeloproliferative neoplasia-associated myelofibrosis. The authors tackle an important issue: inappropriate use of transplants may do harm or deny persons with this serious disease potential benefit. So let's see how this report illuminates the question.

There are many definitions of consensus. For example, for Abba Eban: 'Consensus means that lots of people say collectively what nobody believes individually'. More ominously, for Michael Crichton: 'Historically, the claim of consensus has been the first refuge of scoundrels; it is a way to avoid debate by claiming the matter is already settled'. We agree; not that the authors are scoundrels but that the value of consensus is often over-estimated. Moreover, we have trouble with the way the Delphi process was done despite excellent tutelage. The reference given is to a 1994 publication. However, we and others have published more recent iterations of the RAND-Delphi consensus process using more sophisticated analytical techniques.[2] In this approach one typically generates 100s or even 1000s of iterations by permuting variables panelists propose are informative in the context of decision-making, and then uses iterative processes and recursive partitioning to determine which variables operate and to assign a score. The question usually posed is appropriateness—namely, do the anticipated benefits of the proposed intervention exceed the proposed risks by a sufficient margin such that the intervention should be done? Inappropriateness is defined as the converse. There are always substantial numbers of clinical settings where the proposed intervention is neither appropriate nor inappropriate, and there is always an indication of variance of the score typically expressed as MAD or mean absolute deviation from the median. It is unclear precisely what analytical procedure was followed in formulating the EBMT/ELN consensus recommendations and how sophisticated and up-to-date they were.

Another issue is that the Delphi process followed is static. In the real world, physicians use a Bayesian approach to determine the appropriateness of future interventions relying on response to a prior intervention(s). For example, the appropriateness of a hematopoietic cell transplant in a person with an excellent response to ruxolitinib is different from the appropriateness in someone failing to respond to ruxolitinib or responding but then relapsing regardless of their risk cohort in the Dynamic Plus International Prognosis Staging System or any other prognostic classification system.

The authors state ruxolitinib is indicated pretransplant. However, ruxolitinib has pleiotropic effects including substantial changes in natural-killer and T-cell function, which might adversely impact transplant outcomes, including infection, graft-versus host disease and relapse.[3,4] Two studies are testing the benefit-risk of pretransplant ruxolitinib and it seems prudent to reserve a recommendation until these data are available (the JAKALLO study by the French FIM group (NCT01795677) and the MPD-RC 114 study (NCT01790295)).

Also, the issue most hematologists face in subjects with high-risk disease is not whether to do a transplant, but when. There are no convincing data that doing a transplant earlier in the same subject is better than delaying a transplant until the subject fails other interventions that have lower immediate risks of death. This issue is, of course, best addressed in a randomized trial, but can also be tackled by Markov modeling, such as we and colleagues have done in myelodysplastic syndrome.[5]

Overall, we applaud the effort of Kröger et al.[1] but urge caution in accepting the consensus recommendations at face value. But judge for yourself. As Marcel Proust said: 'Everyone calls clear ideas those at the same degree of confusion as his own.' And don't forget there was consensus at one time the world was flat. It isn't.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Kröger NM, Deeg JH, Olavarria E, Niederwieser D, Bacigalupo A, Barbui T et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. Leukemia 2015; 29: 2126–2133.
2 Gale RP, Park RE, Dubois R, Bitran J, Buzdar A, Hortobagyi G et al. Delphi-consensus panel analysis of appropriateness of high-dose chemotherapy and blood cell or bone marrow autotransplants in women with breast cancer. Clin Transplant 2000; 14: 32–41.
3 Schönberg K, Rudolph J, Vonnahme M, Parampalli Yajnanarayana S, Cornez I, Hejazi M et al. JAK inhibition impairs NK cell function in myeloproliferative neoplasms. Cancer Res 2015; 75: 2187–2199.
4 Parampalli Yajnanarayana S, Stübig T, Cornez I, Alchalby H, Schönberg K, Rudolph J et al. JAK1/2 inhibition impairs T cell function in vitro and in patients with myeloproliferative neoplasms. Br J Haematol 2015; 169: 824–833.
5 Koreth J, Pidala J, Perez WS, Deeg J, Garcia-Manero G, Malcovati L et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol 2013; 31: 2662–70.