EDITORIAL

The great Lazar—a Graft-versus-host-disease patient!

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Graft-versus-host-disease (GVHD) causes significantly morbidity at many levels including from physical effects, which may include disfigurement and compromise to such an extent that psychosocial toxicities follows. It, (like leprosy patients) can affect almost every organ and can lead to devastating effects and therefore has been termed by various investigators over decades as "runting syndrome", "wasting syndrome" etc [1]. It remains the leading cause of non-relapse mortality and morbidity in recipients of allogeneic hematopoietic cell transplantation (allo-HCT) [2]. It causes significant compromise of health-related quality of life (HR-QoL) which has been validated across many countries globally [3]. With a seven-decade history of allo-HCTs, our best efforts to eradicate this condition has culminated in some early successes but the morbidity of the disease remains so crucial that it can lead to a high incidence of post-traumatic-stress-disorder, depression, anxiety issues and also social isolation from friends and social circles [4]. Similar to the lepers, this disruption of social ecosystem leads to many subsequent problems, which we term as "social toxicity".

What is the solution to GVHD and how do we end it? Currently, at least three treatment modalities are approved for steroid refractory (SR) acute GVHD (SR-aGVHD) in various countries which include ruxolitinib [5, 6] in the United States and many other countries, extra-corporeal photophoresis (ECP) [7] in many European countries and mesenchymal stromal cells in gastrointestinal GVHD in pediatric populations in New Zealand, Australia, Japan and Canada [8]. For SR chronic GVHD (SR-cGVHD), approved modalities in various countries include at least four treatments: belumosudil [9], ECP, ibrutinib [10], and ruxolitinib [11]. However, none of these above-mentioned treatments is a panacea, and while ruxolitinib has been shown to have at least a temporary effect, none significantly affect overall survival in a clinically meaningful way. Moreover the exact mechanism of refractoriness of cGVHD remains unknown but proposed mechanisms include significant changes in B-cell signaling, naive T-cell differentiation into type 17 helper T (Th17), type 17 cytotoxic T (Tc17) cells, follicular helper T (Tfh) cells, follicular regulatory T (Tfr) cells, and fibrosis-promoting factors [12].

Thus, prevention of the cGVHD is the key to success for an allo-HCT. There are 2 aspects of prevention when it comes to cGVHD. Primary prevention and secondary prevention. Primary prevention is the use of either graft manipulation or immunosuppressive therapy (IST) to completely abate the risk of GVHD, and secondary prevention is to prevent flares and "relapses". Though the frequency of these flares and/or relapse may be common, just like a myeloma relapsing, the prevention of relapse or a flare of cGVHD is an understudied area.

In this issue of *Bone Marrow Transplantation*, El Jurdi et al. [13] present an institutional study on cGVHD flares. In their study, cGVHD was diagnosed in approximately two-thirds of the recipients of allograft in a 2-year study, and the mean time of flare was about 6 months from diagnosis. Unfortunately, about a third of these patients experienced multiple flares. They also demonstrated that the corticosteroids remained the backbone for the treatment of the flares but half of the patients had another IST added to the anti-GVHD armamentarium. We congratulate the investigators for doing this relatively simple, yet a crucially important study on real-world issue that our patients suffer from.

In their study, none of the clinically important variables which affect the allo-HCT outcomes impacted the occurrence of flare including gender, age, conditioning, type of GVHD prophylaxis, time to cGVHD diagnosis post-HCT, cGVHD severity at onset, or platelet count at diagnosis of cGVHD. The only variable that was associated with statistical significance was quiescent type of cGVHD at onset, which increased the risk of flare by 80%, whereas de-novo and progressive cGVHD were not found to be predictive of flares. Although the overall survival was not impacted by the flares, about half of the entire cohort succumbed to cGVHD per the results.

When the survival is not significantly affected either way, the morbidity due to cGVHD becomes a key aspect of allo-HCT management. The morbidity evaluation by HR-QoL surveys, and more importantly by patient-reported outcome measures (PROM) is of paramount significance in the current patient centered era. The absence of HR-QoL data in cGVHD sufferers, is a huge deficiency of this study, like many other studies in our field of HSCT. Additionally, an important variable is first time IST taper which can potentially change the risk of acute GVHD, de-novo, progressive or quiescent cGVHD. Absence of information of this variable may skew the results towards or away from the occurrence of flares, as the flares themselves were associated with quiescent cGVHD. Another practical concern is that absence of unrelated donors in this cohort, may actually *underestimate* the true risk of both cGVHD and its flares.

Despite the above limitations, the study is one of the first to indicate the importance of cGVHD flares, and though the PROM or HR-QoL data was absent, it can be comfortably predicted that those with active cGVHD (including flares) would have a significantly compromised HR-QoL. Some provocative questions remain unanswered:

(a) What is the optimum time to start taper of IST from the time of allo-HCT?

Conventional wisdom indicated that in the cases of hematologic malignancies, earlier taper is better to incite a graft-versus-tumor effect, however recent data has indicated that in certain groups, early versus late taper does not significantly affect the survival, but affects the rates of cGVHD tremendously. In the current "omics" era molecular studies where minimal residual disease can predict relapse risk, not just in acute lymphoblastic leukemia but also in multiple other hematologic malignancies, it is imperative that taper of the IST be tailored to the relapse risk and in those with complete remission pre-HCT (and no high-risk

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genomics), the IST not be tapered too early [14, 15].

(b) After initiation of treatment for cGVHD, when should one taper the IST? Is it based on the NIH grade of cGVHD, severity of organs affected, HR-QoL, long term adverse effects, or other variables? Should we aim to completely control GVHD symptoms or just to stabilize patient's condition before starting to taper IST? We really do not know and a longer prospective study in various populations is necessary to evaluate external validity.

(c) Is the cGVHD flare incidence (and its pattern) in this study a benchmark for its epidemiology? Perhaps not, since the natural course of the cGVHD can be affected by many factors including institutional practice, and even within institutions, physician practices in tapering IST may be heterogeneous; but we need studies to prove or disprove this notion.

(d) Should we wait for cGVHD to occur and then aggressively treat it with a prolonged course of IST (or a second agent), or majority of the efforts should be directed for prevention of both acute and GVHD by intensified and prolonged IST immediately post-HCT? In the current era of serotherapy and post-transplant cyclophosphamide for prevention of GVHD, one still must consider tapering of IST (e.g., calcineurin inhibitors, sirolimus, MMF etc.) as an important determinant of GVHD occurrence and must be cautious and hyper vigilant for any early signs of cGVHD appearing at taper.

(e) Should we still consider a bone marrow (BM) source in hematologic malignancies which are in reasonable remission, as not only the BM source is associated with significantly reducing the risk of cGVHD, but is also associated with improved PROs at 5 years post-HCT? [16].

We hope that provocative questions can be answered with studies with longer follow up, and can be replicated at other institutions as well. Until then, it is imperative that practicing HCT clinicians try their level best to *prevent* GVHD (and its flares), in order to preserve some HR-QoL of these patients, which is one of the ultimate aims of HCT anyways. Given the novel agents which have been recently approved by the US-FDA for cGVHD e.g., belumosudil and ruxolitinib, we hope that sustained use of these drugs in cGVHD patients (if not causing any significant toxicity), would lead to diminishing of the GVHD flares.

After all, GVHD was, and still remains one of the greatest Lazars of the current century.

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AUTHOR CONTRIBUTIONS

SKH and RR wrote the paper. All authors vouch for the accuracy and contents of the paper. All authors approved the final version of the draft.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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