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EDITORIAL

The NIH consensus criteria for chronic graft-versus-host disease: far more than just another classification

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This invited Editorial Leukemia is addressed at the paper by Cho *et al.*[1] published in this issue of *Leukemia* on the feasibility of using the NIH consensus criteria for chronic graft-versus-host disease.

Chronic graft-versus-host disease (cGVHD), a multi-organ disorder, is the leading cause of late nonrelapse mortality after hematopoietic stem cell transplant. It has been known for many years that although the disease usually manifests itself more than 100 days after transplant, earlier disease onset could occur. More importantly, clinical syndromes with features of typical acute GVHD are increasingly recognized beyond 100 days after hematopoietic stem cell transplant, especially in recent years with the development of the reduced-intensity conditioning regimen.[2] In addition, patients with acute GVHD may progress to developing cGVHD with symptoms of both acute GVHD and cGVHD. For many years, we have used a grading system, developed by the Seattle group,[3] of limited versus extensive GVHD. This study was designed to identify patients needing systemic immune suppression, but it does not capture the severity of individual organ involvement. Although other grading schemes have been proposed (review in Lee SJ[4]) to predict survival following cGVHD, all lack consistent scoring and assessment of each organ involved in determining the overall severity of the disease. Recognizing these limitations, a group of experts led by Dr Pavletic at the National Institutes of Health (NIH) met in 2004 for a consensus conference on cGVHD. As all participants agreed that it was urgently necessary to get rid of the formal definition of cGVHD (any GVHD beyond day 100), the diagnosis and staging working group of the NIH Consensus Development Project on cGVHD[5] proposed standard criteria for diagnosis (Table 1), organ scoring and global assessment of cGVHD severity (see reference 5 for details on how to score organ severity and to assign a severity grade).

To assess the applicability of NIH consensus criteria for cGVHD, Cho *et al.* in this issue of *Leukemia*[1] studied 211 patients who developed GVHD more than 100 days after allogeneic transplantation and who were reclassified using the NIH criteria. Classifications were late acute GVHD (21%), overlap syndrome (30%) and classic cGVHD (49%). Classic cGVHD and overlap syndrome patients ($n=167$) were graded using both the revised Seattle criteria and NIH global scoring. This is the largest study addressing the critical point of what is left with cGVHD using stringent NIH disease criteria. Two other studies have been published on the same subject: one by the Nashville group involving 110 patients[6] and the other by the Minneapolis group involving 54 patients.[7] Classifications in both studies were late acute GVHD (36 and 15%), overlap syndrome (26 and 28%) and classic cGVHD (37 and 57%) (estimates from references 6 and 7, respectively). Despite not being based on the same patient numbers and including different patient, disease and transplant characteristics, one can thus reasonably assume that approximately 20% of patients formally classified as 'chronic' GVHD using the Seattle day 100 landmark could in fact be considered as having features of an acute inflammatory disease. Is that purely semantic? I do not believe so. This means that all estimates currently published in the literature underestimate acute GVHD incidence and overestimate that of cGVHD. This is not of major importance if you are aware of this caveat; however, it is of importance whether you want to use these incidences to calculate the power of a clinical trial or whether you want to search for a statistical link between acute GVHD and cGVHD with relapse (GVL effect), for example.

Table 1 NIH criteria for acute and chronic GVHD

Category	*Time of symptoms*	*Presence of acute GVHD features*	*Presence of chronic GVHD features*
Acute GVHD			
Classic acute	<100 days	Yes	No
Persistent Recurrent Late onset acute	>100 days	Yes	No
Chronic GVHD			
Classic chronic	No time limits	No	Yes
Overlap syndrome	No time limits	Yes	Yes

An intriguing result in Dr Cho's study is the lack of difference in GVHD-specific survival between patients with late acute GVHD and those with classical cGVHD or with the overlap syndrome. Although not using the same statistical tool, this is in sharp contrast with the results of two other studies, both of which showed a worse prognosis in patients developing late acute GVHD (that clearly fits in better with my own clinical practice). However, in the large Korean group study, the pattern of acute GVHD onset was significantly different with respect to GVHD-specific survival with worse survival for patients with recurrent late acute GVHD.

Among patients with overlap syndrome and classic cGVHD, Cho *et al.*[1] multivariate analysis showed that both the NIH severity index and the Seattle group classification were useful in predicting survival and discontinuation of immunosuppressive therapy. Using other methods, the Nashville and the Minneapolis groups also suggest that the new classification of the severity of the disease (mild/moderate/severe) could be useful. However, from the three studies available so far,[1–3] it is not yet clear whether this new classification will be a better discriminator of disease severity than the classical (limited/extensive) Seattle classification, as the mild plus moderate categories seem to need to be collapsed to reach significant differences as compared with the severe category.

In summary, although it might be highly surprising that it has taken decades of allogeneic transplantation, we do now have in hand a powerful definition of what is 'acute' and what is 'chronic' GVHD, an absolute premise for clinical trial design and for reporting clinical results. Concerning the NIH severity index, my own biased belief is that only the two ongoing

randomized trials (both in the US and in Europe) will be able to test its usefulness in predicting the cGVHD-specific survival.

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