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by Dietger W. Niederwieser

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The importance of preparation for or achieving accreditation for small and high volume hematopoietic cell transplantation programs

Dietger W. Niederwieser^{1,2}

¹University of Leipzig, Leipzig, Germany

²Center for Cellular Immunotherapies, University of Pennsylvania & Penn Medicine, Philadelphia, PA

Corresponding author:

Dietger Niederwieser, MD

e-mail: dietger@medizin.uni-leipzig.de; Dietger.Niederwieser@pennmedicine.upenn.edu

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In the current issue Bethge W et al.¹ report evidence of a beneficial survival effect in AML patients transplanted in smaller German centers that are preparing for or have achieved JACIE accreditation. This effect seems to disappear with increasing center volume.

After the first proof of hematopoietic engraftment almost 70 years ago,² a substantial number of patients were treated with Hematopoietic Cell Transplantation (HCT) over the subsequent decade³. However, between 1958 and 1968 only 4 of 203 patients survived. A number of advances in the field were then required to make the concept of replacing a diseased bone marrow with a healthy one finally possible and a worldwide success⁴. After a total of more than 1.5 million procedures at a current rate of more than 100,000 transplants/year and growing, HCT now represents an established treatment with curative potential in a range of diseases⁵.

The establishment of an accreditation quality assurance (QA) system for HCT in Europe (JACIE) and North America (FACT) has been one of the more recent contributions to this success. The beneficial effect of QA system accreditation on outcome was proven in a pivotal study involving 107,904 patients with various hematological diseases transplanted mostly in high volume European centers.⁶ Relapse free survival increased continuously with the attainment of more advanced phases of the accreditation process and reached an overall improvement of 14% after full accreditation. The benefit is of the same order of magnitude as those associated with major innovations in the field such as new immunosuppressive regimens for graft-versus-host prophylaxis.

In a previous publication on the same cohort of adult AML patients only program duration, center volume and non-university hospital centers appeared as significant risk factors for 12 months OS, while the absence of JACIE accreditation was not.⁷ The new evaluation shows that standardized approaches using a QA system such as JACIE, ISO 9001 or others are now routine and that the differences seen 15 years ago have since disappeared in large volume German centers and have been reduced to borderline in those operating at small volume. Good news for our patients! Let's analyze differences between the current German and the pivotal European study. There is a substantial lower number of centers (n=52) and patients (n=5328) in the current

study compared to the 2011 analysis (421 centers and 107,904 patients). An imbalance between the number of patients (n=779) from the 5 larger non-accredited centers as compared to those (n=3,656) from centers already undergoing or granted accreditation may mask statistically significant differences. In addition, the presence of alternative QA may play a role in the 5 non-accredited high-volume centers. But even in the German study the mixed effect cox model quantifies the effect of accreditation on OS with a HR 0.74% while the effect of center volume has a HR 0.99% (Table S1¹). German specific interactions (p=0.04) in exclusively AML patients between accreditation, transplant volume and academic status may challenge subgroup and multivariate analysis. Such interactions were not detected in the 2011 pivotal study on different diseases.

Do we need confirmatory prospective studies on extensive patient numbers to confirm these findings in Europe? Starting from the data exchange that led up to the introduction of the FACT/JACIE-based QA management system two decades ago⁸, the field and transplant programs worldwide have changed. HCT has grown from a regional to a worldwide treatment with graft exchanges in and between low, middle and high income countries. The majority of patients are now transplanted in JACIE/FACT accredited centers and the standardization of QA systems is essential to ensure equity, quality and access in line with the WHO principles. With the new challenges presented by cellular therapies, it is likely that further development of a QA system 4.0 may be needed.⁹

Should accreditation be a target for low or middle income countries as well? Treating patients according to SOPs, either center-specific or provided by a third party, is a first step in the successful establishment of new or optimization of existing programs and in the accreditation process. Few centers, supported by the local scientific organizations Latin America- (LA-), Asian Pacific- (AP-) and African- (AF-) Blood and Marrow Transplantation groups (-BMT) have been already accredited in their respective regions according to reports to the Worldwide Network for Blood and Marrow Transplantation (WBMT). Even if the time needed to achieve the diverse steps of accreditation may vary, outcome is expected to be improved already during the preparation phase.

Is center size really more important than accreditation and should we concentrate only on high volume programs¹⁰? This seems impractical, since low volume centers around the world will continue to be relevant both for geographical and for long-term care reasons. The current study confirms that accreditation, including preparation to a worldwide accepted QA system, provides a justification for low volume centers, even considering the burden on resources involved in achieving the minimum HCT activity stipulated by JACIE/FACT. The conclusion that JACIE/FACT accreditation in high volume centers is being made superfluous by parallel or no QA systems is not supported by the current analysis in Europe and worldwide.

JACIE/FACT is not simply a QA system on organization and procedures, but requires both registration and outcome reporting for all patients receiving cellular therapies as defined and according to uniform and harmonized criteria established by EBMT and CIBMTR. Without these mandatory outcome registries, no credible overview on outcome will be available. Furthermore, accreditation is performed by specially trained inspectors active in institutions performing cellular therapies. This leads to interactions between inspectors and inspected with new insights and new ideas for QA.

The recommendation put forward by the authors of establishing new QA systems with the aim of «...controlling those uncertainties which are likely to be relevant in the real world, and ideally can be proven by scientific evaluation.» is highly questionable. JACIE/FACT are validated QMS systems with current global reach. It seems highly negligent at a time when cellular therapies are expanding and diversifying to renounce JACIE/FACT in the absence of an established alternative.

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