Lenalidomide maintenance after allogeneic HSCT seems to trigger acute graft-*versus*-host disease in patients with high-risk myelodysplastic syndromes or acute myeloid leukemia and del(5q): results of the LENAMAINT trial

We read with interest the recent article by Möllgard *et al.*[1] concerning the efficacy of single agent lenalidomide (LEN) in patients with chromosome 5 abnormalities and advanced myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). In general, allogeneic stem cell transplantation (HSCT) is still the treatment approach with the highest curative potential in these poor-risk patients. However, early relapse rates are still considerably high at up to 50%.[2-3] In fact, there is a substantial need to develop therapeutic strategies aimed at improving long-term outcome after allogeneic HSCT. Implementing LEN in the induction therapy before HSCT, as suggested by Möllgard *et al.*[1] and as also shown by our group,[4] might be one approach to reach higher and more durable response rates in these patients. Another promising strategy could be the use of LEN in the maintenance setting following allogeneic HSCT, as its immunomodulatory properties might enhance graft-*versus*-leukemia (GvL) effects.

Therefore, we designed a prospective phase II trial evaluating the efficacy and safety of early LEN maintenance in high-risk MDS or AML patients with del(5q) cytogenetic abnormalities. From 2008 to 2009, 10 patients with either high-risk MDS (n=1) or AML (n=9) and a median age of 65 years (range 40-72 years) in documented complete remission (CR) after HSCT (Table 1) were recruited from several centers in Germany. LEN maintenance (10 mg/day for 21 days of a 28-day cycle) started at a median of 2.5 months (range 2-4 months) for an expected period of 12 cycles after allogeneic HSCT.

The trial was stopped prematurely, mainly because of the suspicion that LEN was the cause of severe acute graft-*versus*-host disease (aGvHD). In fact, 6 of 10 patients (60%) developed aGvHD grade 3-4 within the first 2 cycles of LEN maintenance. Notably, all patients were still under systemic immunosuppression at that time. Acute GvHD resolved in 4 of 6 patients after discontinuation of LEN and initiation of steroids. Treatment with LEN was later re-started, but reappearance of aGvHD led to permanent discontinuation of treatment in 4 of 6 patients.

Additionally, another 4 patients had to stop treatment prematurely due to relapse resulting in a premature study termination rate of 80%. However, we can not exclude the possibility that treatment delay or complete cessation of LEN due to aGVHD was at least in part responsible for the high relapse rate. Nevertheless, in one patient we observed a significant reduction in $CD34^+$ donor chimerism indicating an impending hematologic relapse[5] during discontinuation of LEN, which converted to a complete $CD34^+$ donor chimerism after re-exposure to LEN (*data not shown*). This suggests a direct clonal cytotoxic or GvL-enhancing effect by LEN. Currently, 5 of 10 patients (50%) are alive and 4 of them are in continuous CR after a median follow-up time of 331 days (range 122-751 days) after HSCT.

The high rate of severe aGvHD in our study is in line with the recently published data by Kneppers[6] and colleagues. They investigated early LEN maintenance at the same dose as in our study in patients with multiple myeloma undergoing allogeneic HSCT and concluded that this approach is not feasible due to increased incidence of acute GvHD.

The immunomodulatory effects of LEN, including T- and NK-cell activation are well known and have been demonstrated in previous studies.[6-8] Quite recently, McDaniel *et al.* found that LEN has the potential to increase the effector function of T cells and can reverse T-cell tolerance in MDS patients.[9] While these immunomodulatory properties have nourished hopes of enhancing the GvL effect following HSCT, it was unclear whether they might influence clinical GvHD. In order to exclude patients at risk of developing severe aGvHD already prior to starting LEN in our study, proteomics of urine samples prior to LEN treatment were analyzed, as previously described.[10] However, we could not detect an aGvHD-specific signature (*data not shown*) in any patient, pointing to an obvious *de novo* induction of aGvHD by LEN.

Our results and those of Kneppers *et al.*[6] are in contrast to previous studies reporting a lower rate of aGvHD during post-transplant LEN treatment,[7,11] but all of these studies used LEN exclusively in myeloma patients with overt relapse after allogeneic HSCT, at later time points than in our study and in combination with steroids, which might

Table 1. Patients' characteristics.

Patient	Disease	Cytogenetic	Donor (sibling/unrelated)	Start LEN (days after HSCT)	Cycles of LEN	Relapse	Maximum aGvHD grade	Cause of treatment discontinuation
1011	AML	del(5q), complex aberration	matched, sibling	90	1	No	bowel III°	aGvhD III°
1012	AML	del(5q), one additional	mismatch*, unrelated	76	5	Yes	skin III°, bowel II°	relapse
1013	AML	del(5q), complex	matched, unrelated	67	4	Yes	bowel III°	relapse
1014	AML	del(5q), complex	matched, unrelated	74	2	Yes	skin III°, mucositis	aGvhD III°
1015	AML	del(5q), one additional aberration	matched, unrelated	68	3	Yes	0	relapse
1021	RAEB 1	single del(5q)	matched, unrelated	114	12	No	skin I°	regularly
1041	AML	single del(5q)	matched, sibling	63	12	No	0	regularly
1042	AML	single del(5q)	matched, sibling	69	1	No	skin III°	aGvhD II°
1061	AML	del(5q), complex	mismatch**, unrelated	108	5	Yes	0	relapse
1081	AML	del(5q), complex	mismatch**, unrelated	111	5	No	bowel III°	aGvhD III°

**one allele mismatch, ** antigen mismatch. AML: acute myeloid leukemia; LEN: lenalidomide; HSCT: allogeneic stem cell transplantation; aGVHD: acute graft* versus *host disease.*

have further abrogated the potential effects of LEN. On the other hand, due to the fact that LEN is a derivative of thalidomide, it seems surprising that the latter has already been successfully used in the therapy of chronic GvHD.[12] One explanation could be that the immunmodulation of T- and NK-cells by IMIDs might have different effects during different posttransplantation phases. Therefore, in future studies a delayed initiation of LEN maintenance might potentially be associated with lower rates of aGvHD.

In conclusion, we demonstrate that early LEN maintenance at a dose of 10 mg/die to prevent relapse following allogeneic HSCT is not feasible, mainly due to the induction of severe aGvHD. Whether lower doses or a delayed initiation of LEN maintenance therapy (6-12 months following HSCT) could make this approach more feasible has to be evaluated in future prospective trials. Since patients with MDS and myeloma are generally considered to be at high risk for aGvHD, these studies will have to be designed carefully, with particular attention to frequent monitoring of any emergence of aGvHD.

Katja Sockel,[1] Martin Bornhaeuser,[1] Eva Mischak-Weissinger,[2] Rudolf Trenschel,[3] Martin Wermke,[1] Christian Unzicker,[4] Guido Kobbe,[5] Jürgen Finke,[6] Ulrich Germing,[5] Brigitte Mohr,[1] Jochen Greiner,[7] Dietrich Beelen,[3] Christian Thiede,[1] Gerhard Ehninger,[1] and Uwe Platzbecker[1] on behalf of the German MDS and Cooperative Transplant Study Group (GCTSG)

[1]Medical Clinic and Policlinic I, University Hospital Dresden; [2]Department of Hematology/ Oncology, Hannover Medical School; [3]Department of Bone Marrow Transplantation, University Hospital Essen; [4]Department of Internal Medicine II, Wuerzburg University Medical Center; [5]Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine-University of Düsseldorf; [6]Department of Medicine 1, Hematology/ Oncology, University Hospital Freiburg; [7]Department of Internal Medicine III, University of Ulm, Germany

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Correspondence: Uwe Platzbecker, Universitätsklinikum Carl-Gustav-Carus, Medizinische Klinik I, Fetscherstraße 74, 01307 Dresden, Germany. Phone: international +49.351.4582583; Fax: international +49.351.4584373; E-mail: uwe.platzbecker@uniklinikum-dresden.de

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