Leukemia (2019) 33:588–596
https://doi.org/10.1038/s41375-019-0383-2

REVIEW ARTICLE

Multiple myeloma gammopathies

Is lenalidomide the standard-of-care after an autotransplant for plasma cell myeloma?

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Received: 22 June 2018 / Revised: 21 September 2018 / Accepted: 28 September 2018 / Published online: 28 January 2019

Abstract

Three randomized controlled trials and a meta-analysis reported lenalidomide given after high-dose therapy and an autologous hemopoietic cell transplantation is associated with increase in progression-free survival (PFS) and survival in persons with plasma cell myeloma (PCM). Based on these data, posttransplant lenalidomide is considered by many a standard-of-care in this setting. However, decisions on the use of new therapies should consider not only results of such trials and meta-analyses but also other factors including quality-of-evidence, anticipated desired and undesired effects of the drug, costs and feasibility of the therapy option. In this review, we critically analyzed evidence on posttransplant lenalidomide in PCM, and we identified criteria which should be considered in designating posttransplant lenalidomide the standard-of-care. Using Grading of Evidence, Assessment, Development and Evaluation (GRADE) approach we judged posttransplant lenalidomide improves PFS with high-quality evidence. However, we identified inconsistency and imprecision as limitations in the conclusions regarding a survival benefit rating the quality-of-evidence for a survival benefit moderate. We also highlighted inconsistency in claims of an increased risk of new cancers associated with posttransplant lenalidomide. We emphasize the need for a value-based reasoning which considers PFS and survival as well as health-related quality-of-life and costs. We conclude the decision to use posttransplant lenalidomide should be individualized based on pre- and posttransplant variables such as remission state, risk category and/or posttransplant measurable residual disease (MRD)-test results. Validity of these variables in estimating benefits and risks of posttransplant lenalidomide should be tested in randomized clinical trials.

Introduction

High-dose chemotherapy and an autotransplant is widely used to treat persons with plasma cell myeloma (PCM). Several randomized clinical trials (RCTs) report improved progression-free survival (PFS) and survival compared with other post-induction therapies [1–7]. However, despite these advantages, most autotransplant recipients relapse and die of recurrent disease. Consequently, interventions to prevent relapse are needed.

Lenalidomide is an immune-modulating drug (IMiD®) active in PCM. In a phase-2 study, posttransplant lenalidomide was reported to upgrade responses [8]. Randomized trials report posttransplant lenalidomide significantly prolongs PFS and possibly survival [9–11]. Based on these data, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved posttransplant lenalidomide in persons with newly diagnosed PCM receiving an autotransplant. Additionally, many experts recommend maintenance lenalidomide in persons failing to achieve very good partial response posttransplant [12]. The National Cancer Comprehensive Network (NCCN) guidelines (version 3.2017) lists lenalidomide as a preferred posttransplant regimen [13].

McCarthy and coworkers published a systematic review of RCTs of posttransplant lenalidomide using subject-level data from 1208 subjects receiving or not lenalidomide [14]. The authors concluded posttransplant lenalidomide is associated with significant survival benefit. Based on these new data, the European Society of Medical Oncology

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(ESMO) Multiple Myeloma Guidelines Committee recommended maintenance lenalidomide after an autotransplant [15], a recommendation seconded by others [16]. The most recent version of NCCN guidelines lists lenalidomide is the standard posttransplant approach of PCM [17].

The decision to give posttransplant lenalidomide is complex. The DECIDE project recommends a systematic transparent approach to making well-informed health care choices. These experts recommend decisions on the use of a new therapy consider many variables including quality-of-evidence, anticipated desired and undesired effects of the intervention, costs and feasibility of the therapy option [18, 19]. Deciding whether to give posttransplant lenalidomide requires a critical appraisal of these variables. In this review, we followed the DECIDE recommendations. We critically appraised evidence on posttransplant lenalidomide in PCM using the Grading of Evidence, Assessment, Development and Evaluation (GRADE) approach [20]. We also considered criteria which should be considered in the context of recommending posttransplant lenalidomide.

Critical appraisal of evidence

We searched the PubMed and Embase databases from 1 January 2011 through 31 March 2018, using controlled vocabulary descriptors and specific keywords to represent the concept of PCM and use of lenalidomide to identify RCTs of posttransplant lenalidomide. We searched only for randomized studies; phase-1/-2 uncontrolled studies, observational studies and studies reported only as an abstract were not included in the analyses. The search was augmented by manual searches of reference lists from potentially relevant papers to identify studies missed using the computer-assisted strategy. Three RCTs and the meta-analysis met the eligibility criteria and are reviewed in detail (Table 1) [9–11, 14].

Risk of bias (internal validity)

We first analysed the 3 RCTs for the internal validity (i.e. risk of bias inherent to the trial-design) using the Cochrane Collaborations risk of bias assessment including adequacy of sequence generation, allocation sequence concealment, level of blinding, incomplete outcome data, selective outcome reporting, incomplete reporting for loss to follow-up, and stopping early for benefit components [21].

Subjects in the GIMEMA trial were randomly assigned at enrollment but the results of the random assignment were concealed until subjects reached the end of the induction period [11]. As such, the trial was not blinded for the maintenance phase. However, frequencies of subjects

Table 1 Randomized controlled trials analyzed in the critical appraisal of evidence

Study [reference]	Population	Induction, consolidation	Maintenance	*N*	Median follow-up (months)
Intergroupe Francophone du Myeloma (IFM) trial. [9]	<65-year-old, transplant eligible	VAD or BOR/Dex, ASCT (1 or 2)	Lenalidomide (10 mg/d for 3 months followed by increase up to 15 mg/d if tolerated until relapse) Placebo	307 307	60
Cancer and Leukemia Group B (CALGB) trial [10]	<70-year-old, transplant eligible	Various, ASCT	Lenalidomide (10 mg/d until progression) Placebo.	231 229	65
Gruppo Italiano Malattie Emotologiche dell'Adulto (GIMEMA) trial [11]	>65-year-old, transplant eligible	MPR MPR MP	Lenalidomide Placebo Placebo	88 94 102	65

VAD Vincristine, doxorubicin, and dexamethasone, *BOR/Dex* bortezomib and dexamethasone, *ASCT* autologous stem cell transplantation, *MPR* melphalan, prednisone and lenalidomide, *MP* melphalan and prednisone

discontinuing maintenance lenalidomide for reasons other than disease progression or toxicity were 9% in the lenalidomide cohort and 3% in controls ($P = 0.06$), suggesting low probability for an attrition bias. We also considered the published protocols to assess the potential for selective outcomes reporting bias. The GIMEMA study publication reported results of analyses of PFS, survival and adverse events but not quality-of-life, response duration or time to next therapy all of which were specified in the protocol. These data indicate selective reporting bias.

According to GRADE reporting bias should be suspected if a study publication fails to report outcomes one would expect [22]. Health related quality-of-life (HRQoL) is an increasingly important outcome dimension [23]. However, none of the 3 RCTs reported data on this endpoint. Another outcome one would expect but which is not reported in any trial is *s*econd progression-free survival (PFS2) [24]. The McCarthy meta-analysis reported time to second-line anti-myeloma treatment and PFS2 [14]. Time to second line anti-myeloma treatment was prolonged with maintenance lenalidomide versus controls (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.49, 0.66). Median PFS2s were 73 months versus 57 months (HR, 0.72; 95% CI, 0.62, 0.84). These data offset a reporting bias in the trial reports.

In conclusion, using GRADE methodology we determined the 3 RCTs present a risk of bias from selective reporting (Fig. 1). However, this risk was deemed moderate and we judged this bias does not undermine the overall quality-of-evidence.

	Random sequence generation	Allocation concealment	Blinding of partecipants and personell	Blinding of outcome assessment	Selective reporting	Large losses to follow-up	Stopping early for benefit
IFM (2012)[9]	No	No	No	No	Yes	No	No
CALGB (2012)[10]	No	No	No	No	Yes	No	No
GIMEMA (2014)[11]	No	Yes	Yes	Yes	Yes	No	No

Fig. 1 Risk of bias summary

Rating quality of evidence (external validity)

We rated the quality-of-evidence of the three RCTs by evaluating whether their results could be reasonably applied to persons with PCM after high-dose therapy and an autotransplant. Four dimensions of evidence were analysed: imprecision; inconsistency, indirectness, and publication bias. Using the GRADE framework, we graded confidence in effect size estimates starting as high, and potentially decreasing as the quality of evidence declined.

PFS was the primary outcome of the trials and sample sizes were calculated for this endpoint. We used confidence intervals (CIs) of the effect size as the primary tool for judging precision of outcomes [25]. The 95% CI informs the impact of random error on evidence quality and establishes the range of plausible results. In the trials, the higher boundary of the HR for PFS closest to no effect (HR = 1) ranged from a 45 to 53% reduction in the risk of progressive disease in subjects receiving posttransplant lenalidomide. Based on these data, we consider precision of PFS of lenalidomide effect size high.

Two trials reported improved survival in persons receiving posttransplant lanalidomide compared with controls but only the CALBG trial reported a statistically significant benefit. Heterogeneity in treatment-effect on survival remained despite longer follow-up of the IFM and GIMEMA trials in the meta-analysis [14]. At the cut-off date of the meta-analysis only the CALBG study had a significant survival benefit (HR = 0.56; CI, 0.42–0.76). These data highlight inconsistency of the results that could potentially downgrade the quality-of-evidence.

We searched for possible reasons for this heterogeneity. One was different therapy durations. Median durations of posttransplant lenalidomide in the CALGB and GIMEMA studies were 30 and 36 months versus 25 months in the IFM study. In multivariate analyses survival heterogeneity resulted mostly from differences between CALBG and IFM studies [14]. Longer treatment duration in the GIMEMA study compared with the IFM study did not result in a significant improvement in survival compared with controls. Consequently, it seems unlikely different therapy durations explain the heterogeneity of survival results. We conclude inconsistency of survival outcomes is an important, unresolved limitation of concluding posttransplant lenalidomide improves survival.

In the McCarthy meta-analysis with a median follow-up of 6.6 years median survival of subjects receiving posttransplant lenalidomide was not reached compared with 82 months in controls (HR = 0.74; 95% CI, 0.62, 0.89) [14]. The upper boundary of the confidence interval closest to no effect is a 11% reduced risk of death. Without objective criteria for evaluating the clinical relevance of this

Table 2 Evidence profile: posttransplant lenalidomide therapy versus no therapy or placebo for plasma cell myeloma[a]

Outcomes	Participants (studies) – follow-up	Quality of evidence (GRADE)	Relative effect (95% CI)	Risk with lenalidomide	Risk with placebo-no therapy
Mortality	1208 (3 RCTs) – median, 79.5 months	Moderate for imprecision and inconsistency	Hazard ratio, 0.75 (0.63–0.90)	215 events/605 patients	275 events/603 patients
Progression-free survival	1208 (3 RCTs) – median, 79.5 months	High	Hazard ratio, 0.48 (0.41–0.55)	316 events/605 patients	411 events/603 patients
New cancers	1053 (2 RCTs)	Moderate for inconsistency	Relative risk, 4.53 (1.74–11.84)	23 events/530 patients	5 events/523 patients

RCT randomized controlled trial

[a]Data come from the meta-analysis of McCarthy [14]

risk reduction, we judged a survival benefit as being at the borderline limit of precision.

Analysis of the trials revealed differences between the treatment protocols which could have impacted reported outcomes. Induction therapies in the CALGB trial included thalidomide and lenalidomide whereas the IFM trial excluded these therapies. No post-induction, pretransplant nor posttransplant consolidation therapies were given in the CALGB trial whereas all subjects in the IFM trial received two cycles of posttransplant lenalidomide consolidation. In the GIMEMA trial subjects were randomized to consolidation with high-dose melphalan and an autotransplant or to melphalan-prednisone-lenalidomide. Importantly, crossover was allowed in the CALGB trial for subjects randomized to placebo who progressed but not in the IFM trial. A tandem transplant was done in 21% of subjects in the IFM trial but none in the CALBG or GIMEMA trials. These differences do not represent indirectness in the pre-randomization study populations which might influence analyses of outcomes of lenalidomide maintenance.

Because not all persons can receive posttransplant maintenance therapy we defined the population of interest as subjects with a good posttransplant response. We assessed how closely subjects enrolled in the trials resemble persons of interest. In the IFM trial subjects were eligible if they had not progressed in the interval between their last transplant and randomization. Sixty-three percent of these subjects had a very good partial response. In the CALGB trial subjects could be randomized if they did not progress <100 days posttransplant. Responses at transplant were complete, 29%, partial, 50%, and marginal, 5%. In the GIMEMA trial lenalidomide maintenance was started ≤3 months after completing consolidation therapy without disease progression. We conclude there was no indirectness in the study populations included in the trials as far as their indication in posttransplant maintenance therapy.

In summary, because of inconsistency and imprecision, we rated the quality of evidence of a survival improvement from posttransplant lenalidomide as moderate (Table 2).

Authors of the CALBG and GIMEMA trials performed pre-specified sub-group analyses to identify subjects most likely to benefit from posttransplant lenalidomide including: (1) prior induction therapy with thalidomide or lenalidomide; (2) response to induction therapy; (3) response to transplant(s); (4) disease stage at diagnosis; and (5) high-dose melphalan or melphalan, prednisone and lenalidomide for induction therapy. A more extensive sub-group analysis was reported from the McCarthy meta-analysis. Results of sub-group analyses of PFS consistently favored lenalidomide maintenance versus placebo/observation. In contrast, the magnitude of survival benefit for lenalidomide maintenance was heterogenous. For example, a survival benefit was detected in subjects ≤stage-2 at diagnosis but not in

those stage-3. Similarly, a survival benefit was detected in subjects with the deepest posttransplant responses compared with subjects with inferior responses.

Hematological and non-hematological adverse events were more frequent in subjects receving posttransplant lenalidomide compared with controls [9–11]. Because of concern with new cancers, we assessed the quality of evidence supporting this concern. Two trials reported a higher incidence of new cancers in the posttransplant lenalidomide cohort; one did not [9–11]. In the meta-analysis, treatment-emergent adverse events were analyzed for subjects in the two trials originally reporting an increased incidence of new cancers. Cumulative incidence of new hematological cancers was higher in posttransplant lenalidomide cohort compared with controls (HR, 2.03; 95% CI, 1.14, 3.61). There was no difference in cumulative incidence of new non-hematological cancers.

We analyzed data on new cancers to evaluate the effect of inconsistency on the quality-of-evidence from the RCTs. In a meta-analysis of subject-level data from 7 trials in persons with newly-diagnosed PCM receving or not receving lenalidomide, subjects receving lenalidomide had an increased risk of new hematological cancers, predominantly in those receiving lenalidomide and melphalan [26]. In the NCRI Myeloma XI trial of newly diagnosed transplant-eligible and -ineligible subjects no increase in new hematologic cancers was detected with long-term lenalidomide [27]. A cohort analysis and nested case-control study of 1653 newly diagnosed subjects receving lenalidomide without melphalan, reported no increased risk of new cancers [28]. In another study of subjects with advanced PCM receiving lenalidomide and dexamethasone, increasing age and numbers of prior therapies but not lenalidomide exposure were associated with risk of a new cancer in multivariate analysis [29]. The Connect MM, a US-based, multi-center, prospective observational database study reported no significant differences in 3-year cumulative probabilities of new cancers between any of four exposure comparison cohorts [30].

In conclusion, analyses of the 3 RCTs with posttransplant lenalidomide showed inconsistent results of incidence of new cancers. Meta-analysis of 2 trials, did failed to resolve this inconsistency. Because data from indirect studies were also heterogeneous we judged evidence posttransplant lenalidomide increases the risk of new cancers as of only moderate quality (Table 2).

From critical appraisal of evidence to practice recommendations

Use of posttransplant lenalidomide is increasing, likely because physicians and decision-makers argue for a positive balance of benefits versus adverse effects [31]. To weight the strength of this argument we analyzed the validity of this decision reasoning in the light of current evidence.

Balancing benefits and adverse effects considering evidence

There are no widely accepted cancer guidelines defining the magnitude of benefit needed to recommend an intervention [32]. However, operational models suggest criteria for defining the clinical relevance of a new therapy. Sobrero and coworkers conceptualized the increase in survival which balances harms and costs of a therapy as a threshold, called the minimum clinically meaningful outcome (mCMO) [33]. In their model, the extent of the benefit identifying mCMO is a function of three variables: (1) a person's prognosis; (2) toxicity and inconvenience; and (3) cost. For each of these variables the authors arbitrarily set the bar of the mCMO at three different levels of required benefit. The 86 month-median survival of persons candidates to receive posttransplant lenalidomide is in a favorable prognosis category [15, 34]. Treatment-emergent adverse events in subjects receving posttransplant lenalidomide in RCTs resulted in a discontinuation in 29% of subjects [14]. Based on these data, posttransplant lenalidomide requires a high-level of benefit, arbitrarily defined as a survival HR of ≤0.70 [33]. The survival HR of 0.75 reported in the McCarthy meta-analysis is above this threshold resulting in a recommendation against universal use of posttransplant lenalidomide. Furthermore, because the 0.75 survival HR of posttransplant lenalidomide is only of moderate quality evidence (see above) the GRADE philosophy dictates the strength of the recommendation against posttransplant lenalidomide should be graded strong. The same threshold approach we used for balancing benefits and adverse effects of posttransplant lenalidomide is used by the European Society for Medical Oncology (ESMO) to stratify the magnitude of clinical benefit that can be anticipated for anti-cancer therapies [34]. Likewise, a similar survival HR threshold is used by the American Society of Clinical Oncology (ASCO) Cancer Research Committee [35].

Value-based decision making

Decision-makers involved in producing guidelines might disagree with conclusions of the above threshold-based survival HR model. They might argue the model produces drastically different decisions from outcomes data which differ just slightly because of moderate strength of evidence or different decision perspectives. For example, the 0.56 survival HR in the CALBG trial meets the 0.70 threshold. Moreover, the 95% confidence interval of the survival HR in the McCarthy meta-analysis is 0.62–0.89.

If the correct value is the lower boundary posttransplant lenalidmide would be strongly recommended whereas if it is the upper boundary it would not be recommended. Also, the calculation of the survival HR assumes proportional hazards of death. Visual examination of the survival curves in the McCarthy meta-analysis shows non-porportional hazards violating the assumption of the HR calculation. We suggest restricted mean survival time as a better measure of the potential survival benefit of posttransplant lenalidomide. Such a calculation is not reported. An additional consideration is that an arbitrary survival HR threshold ignores the absolute increase in survival. For example, when median survival is 6 months a HR of 0.70 translates to an absolute survival increase of about 2 months. However, when median survival is 7 years (controls in the McCarthy meta-analysis) a HR of 0.70 translates to an absolute survival increase of more than 2 years. If we assume a therapy has the same cost in both scenarios the quality-adjusted life-years (QALYs) are extraordinarily different. Also, uncertainty in the increased risk of new cancers could reset the threshold of worthwhile benefit to moderate-risk which in the Sobrero model requires a survival HR = 0.75 [33]. All these adjustments would result in a recommendation in favor of posttransplant lenalidomide. This model instability undermines the objective of reaching an optimal recommendation based only on survival data.

A more stringent criticism to the threshold decision model, is that a simple reasoning strategy based on a survival HR fails to reflect the complexity of decision-making which includes clinical values, patients' and doctors' preferences, and social constrains. From this perspective, the decision regarding posttransplant lenalidomide becomes more complex and considerably more information is needed to exploit a value-based decision reasoning model.

Posttransplant therapy might impact HRQoL. There are few analyses of this issue [36, 37]. Stewart and coworkers reported posttransplant thalidomide and prednisone negatively affected HRQoL in global, cognitive, and role function domains for many symptoms [38]. Data from the Connect MM registry in 1493 subjects reported no statistically significant changes in the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM), Trial Outcome Index (TOI), and PCM subscale scores in cohorts receving or not receving posttransplant lenalidomide [39].

These data suggest posttransplant lenalidomide is not associated with a substantial decrease in HRQoL and might improve global HRQoL by reducing time spent in disease progression. There are no data to account for a potentially decreased HRQoL because of new cancers associated with giving posttransplant lenalidomide.

Therapy of PCM is expensive [40]. The optimal duration of posttransplant lenalidomide is unknown and might reasonably continue until disease progression. This strategy would result in high costs [41]. In countries with a public health system, these costs could impact on National Health Service budget. Consequently, it is important to set priorities for funding the health care programs and for policy making using cost-effectiveness analyses. These analyses examine overall value of a therapy in terms of incremental costs compared with incremental health benefits. The high costs of posttransplant lenalidomide can be detrimental to person's personal finances and to society [42]. Consequently, from the health care system and clinical perspective, economic assessment quantifying the value of maintenance lenalidomide is needed.

Jakson and coworkers examined the fiscal impact of posttransplant lenalidomide in the context of an evolving and complex therapy pathway. A cost model was developed to compare direct costs over 5 years posttransplant from the perspective of national healthcare providers. Costs considered included drug acquisition, administration and management of adverse events. In the base case, direct medical costs per patient for posttransplant lenalidomide were €209,600 over the 5-year period compared with €276,900 for controls, a 24% saving for giving posttransplant lenalidomide. Moreoover, this analysis did not consider resource savings likely achieved with posttransplant lenalidomide making this saving a conservative estimate [43]. Results of this and other cost-analyses suggest posttransplant lenalidomide reduces the overall direct medical costs and spreads management costs more evenly easing the economic burden for the healthcare system [44].

Multi-criteria therapy reasoning is computationally best-suited through decision models by which pairs of different therapies with different effects, e.g. quality of life, survival, adverse effects, and costs, determine which therapies are most valued. Consequences of different therapies are formalized by health states and the utility of being in a health state is reflected by the scaled HRQoL of an individual at a point in time and costs incurred in that state. The value of such decision reasoning is shown by the UK National Institute for Health and Clinical Excellence (NICE) model which uses multi-state models to evaluate new therapies. For example, lenalidomide and dexamethasone was compared with dexamethasone only for therapy of advanced PCM. In this model, the incremental cost effectiveness ratio was £30,153 per quality adjusted life years (QALY) for the combination, including the costs of therapy, adverse events and disease-follow-up [45]. This ratio is considered highly favorable.

Towards individualized therapy

A multi-state model of value-based decision reasoning is the most clinically appropriate tool to evaluate the appropriateness of posttransplant lenalidomide in persons with

PCM. With this model, decision-makers and experts gain criteria to produce recommendations based on evidence and deep reasoning. However, peoples' hopes for long-term survival and possibly cure depend not only on physicians using a new therapy such as posttransplant lenalidomide but also considering advances in the context of a person's unique biological features. This strategy, sometimes referred to as personalized or precision medicine, requires a new therapy be given only to persons most likely to benefit. Outcome of persons with PCM receiving an autotransplant are heterogeneous and are associated with three predictive variables: (1) depth of the posttransplant response; (2) results of posttransplant measurable residual disease (MRD) testing; and (3) pretransplant cytogenetics [14, 46–48]. Accuracy of these variables to predict cohort-level outcomes is high in analyses of subgroups in clinical trials [14], and in observational studies [47]. However, the predictive value of these variables needs validation that may be exploited with the use of integration and focus of different clinical studies and testing.

Determining whether individualized decision regarding posttransplant lenalidomide is appropriate using well-designed clinical trials is challenging. The open-label, multi-center, MM5 randomized trial from the German-Speaking Myeloma Multicenter Group (GMMG) is testing whether this strategy improves PFS and/or survival in persons achieving a complete remission posttransplant [49]. An updated analysis of the Myeloma XI trial is testing whether posttransplant lenalidomide improves outcomes for newly diagnosed persons according the cytogenetic risk cohort [50]. Results of these studies should inform appropriateness of statistical hypotheses calling for an individualized approach.

Conclusion

In this review we consider the complexities in determining whether posttransplant lenalidomide should be the standard-of-care in persons receiving an autotransplant for PCM. We provide elements needed to construct evidence- and reasoning-based practice recommendations. We explored many facets of this question. We believe more data on HRQoL and costs are needed for value-based decision-reasoning. We suggest new studies and possibly clinical trials are needed to determine appropriateness of post-transplant lenalidomide at the subject-level and to accurately identify persons most likely to benefit. We are aware achieving this goal is unavoidably complex. However, PCM is also complex biologically, clinically, socially, and economically. And people with this disease are equally or more complex. We argue solving these complexities requires cooperation between diverse stakeholders. This review represents a template of how clinical investigators should offer the tools for providing the best recommendation on using lenalidomide posttransplant.

Acknowledgements We are responsible for the views expressed and do not represent the views, decisions, or policies of the institutions with which they are affiliated. Prof. Mohammed Hussein (Univ. South Florida and Celgene Corp.) kindly reviewed the typescript and made helpful suggestions.

Compliance with ethical standards

Conflict of interest GB received advisory board funds from Novartis. RPG is a part-time employee of Celgene Corp.

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