EDITORIAL

Relapsed systemic light chain amyloidosis – in search of a higher bar

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The primary aim in the management of systemic light chain amyloidosis (SLCA) is the rapid achievement of deep hematologic response and ultimate reversal of any organ dysfunction caused by the deposition of amyloidogenic light chains. Cytogenetic abnormalities such as t(11;14) and other biologic features including excess plasma cells have been described as adverse prognostic factors in AL amyloidosis, impacting the hematologic response rate and overall survival (OS), but there is little known about any other factors that predict for, or against, hematologic relapse after frontline treatment with autologous stem cell transplantation (ASCT) in SLCA. *Zhang* et al. present a retrospective analysis from China between 2010 and 2021, in which they set out to describe risk factors, potential treatment, and outcomes of patients with SLCA who relapse after ASCT [1]. They report that lambda restricted, difference between involved free light chain (iFLC) and uninvolved free light chain (dFLC) > 30 mg/L pre ASCT, reduced dose melphalan and dFLC >10 mg/L at 6 months after ASCT were independent risk factors for relapse, while achieving complete hematologic response (CHR) after induction and having a renal response after ASCT were protective factors against disease relapse. They further show that patients receiving bortezomib or daratumumab salvage therapy showed a better survival compared to other chemotherapy regimens [1].

Like any retrospective effort, their study is marked by bias with regards to patient selection, as well as lack of further explanation why certain patients were unevaluable for response and were excluded from analysis. Their cohort also appears to be particularly enriched for patients who had renal involvement (100%), which is significantly higher than a general incidence of 50%–70% seen at the time of clinical presentation, however this is likely explained by the fact that the study was conducted at the renal disease center [2]. Other organ involvement is additionally reported on cardiac and hepatic involvement only. Importantly, no patients in their cohort received daratumumab based induction therapy, though this too is somewhat understandable given the timeframe of the study (2010 to 2021) in the context of the US Food and Drug Administration (FDA) granting accelerated approval to daratumumab and hyaluronidase-fihj in combination with bortezomib, cyclophosphamide, and dexamethasone (DVCd) for the treatment of newly diagnosed SLCA in January 2021 [3]. We also lack baseline information on all patients in terms of presence of any high-risk cytogenetics such as t(11;14) or any patients with multiple myeloma (MM) component by lytic lesions on skeletal imaging, both of which have been described as predictors of early treatment failure and of poorer survival in newly diagnosed SLCA patients [4, 5].

Also notable is the fact that the 94 patients in the control arm who received 81.9% bortezomib-based induction achieved CHR at a significantly higher rate (37.3%) than what has been reported in other phase 3 studies with bortezomib-based induction studies: efficacy of bortezomib, cyclophosphamide and dexamethasone (VCd) in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III) in international, multicenter series of 60 patients showed a CHR rate of 25% [6]; in the largest study to examine the efficacy of the VCd regimen which was a European retrospective series of 230 newly diagnosed AL amyloidosis patients, authors reported 23% CHR rate [7].

About 40% of patients in the relapse group and 18% of patients in the control group received additional consolidation chemotherapy, though the indications for additional consolidation in these patients remain unclear. Furthermore, since the 35% of the patients in the relapse group received a reduced dose of melphalan, further insight into the reasons behind the dose reduction would provide valuable insight into the potential confounding issues surrounding the outcomes of these patients. What similarly remains unclear is if the full-dose melphalan was associated with lower risk of relapse even in those patients who achieved a deep response (≥VGPR) to induction prior to ASCT consolidation.

Median OS in SLCA has progressed steadily over the last 4+ decades, to three times median survival of 4.6 months for the era of this study (2010–2019) compared to where we were in the 1980s [8]. Unlike in MM, considering that life-threatening organ dysfunction can still be occurring in the presence of low-level amyloidogenic light chains, the most important endpoint following induction therapy in SLCA, whether ASCT containing or not, is normalization of the serum-free light chain and attainment of minimal residue disease (MRD) negativity. Our ability to achieve these deep responses has become drastically better after the maiden SLCA FDA drug approval of daratumumab and hyaluronidase-fihj in DVCd combination for newly diagnosed patients. In the pivotal ANDROMEDA study, which randomly assigned patients with newly diagnosed AL amyloidosis to receive 6 cycles of VCd either alone (control group) or with subcutaneous daratumumab followed by single-agent daratumumab every 4 weeks for up to 24 cycles (daratumumab group), the attainment of a hematologic CR which was a primary endpoint was significantly higher in the quadruplet vs the triplet arm: 53.3% vs 18.1%, respectively [9]. This response superiority deepened even further to 60% vs 19%, respectively, after median follow up of 25.8 months [10]. The ability to achieve this unprecedented level of responses to extended induction therapy alone has raised the question of whether ASCT consolidation can be obviated for some patients in the modern age of SLCA treatments [11].

So far, including the current study by *Zhang* et al., literature has identified several post-treatment factors relating to the depth of response in the iFLCs or the dFLCs, that predict disease relapse, but none of these efforts have been systematically analyzed in the above daratumumab era of the last few years, which has given us an expanded capacity to achieve deep hematologic responses

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Table 1. Relevant phase 3 randomized studies incorporating anti-fibril monoclonal antibodies to the frontline treatment of systemic light chain amyloidosis.

Study Name	ClinicalTrials.gov Identifier	Estimated Enrollment	Randomization	Masking	Primary Endpoint
A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment Naïve Patients With Mayo Stage IIIa AL Amyloidosis	NCT04512235	267	2:1 experimental to control	Quadruple: Participant Care Provider Investigator Outcomes Assessor	Time to All-cause Mortality
A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment Naïve Patients With Mayo Stage IIIb AL Amyloidosis	NCT04504825	124			Time to All-cause Mortality or to the end of the PETP
A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs. Placebo Plus Standard of Care in Mayo Stage IV Subjects With Light Chain (AL) Amyloidosis	NCT04973137	150			Time to All-cause Mortality

AL light chain; *PETP* primary evaluation treatment period.

[1, 12–14]. Some of the more recent studies reporting on the impact of iFLC post treatment and its impact on outcomes in SLCA have included a smaller proportion of daratumumab-treated patients (17%), though none is more thoroughly related to the current practice patterns than the analysis of absolute reduction of the iFLC and the dFLC in the ANDROMEDA study, where authors conclude that regardless of the criteria used, the addition of daratumumab to VCd increased the rates of deep hematologic responses, which, in turn, was associated with prolonged major organ deterioration progression-free survival [15, 16].

Nevertheless, much like in multiple myeloma (MM), and considering that CHR does not always translate into organ response in SLCA, we are continuing to explore deeper response endpoints such as MRD. It seems conceivable that various forms of MRD assessment based on next-generation flow or next-generation sequencing might unify the predictive nature of iFLC and dFLC hematologic parameters towards a simplified tool that can inform on both management decisions and long term predictive outcomes, including improved organ response in SLCA [17].

We are still gathering insights into the dynamics and the manner of disease relapse in the modern times. We are on the precipice of another revolutionary step in the SLCA with several phase 3 trials about to report initial findings on the impact of incorporation of anti-fibril antibodies added to the bortezomib-based induction in the newly diagnosed SLCA (Table 1). The next decade of advancements in the upfront management of SLCA promise to usher new frontiers in terms of our ability to induce deep hematologic and organ responses, which together with MRD assessment tools will undoubtedly create a new, higher bar of excellence we will aim to uphold and surpass.

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AUTHOR CONTRIBUTIONS

MB conceived and wrote the manuscript. SMS helped edit the manuscript.

COMPETING INTERESTS

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