Daratumumab after allogeneic hematopoietic cell transplantation for multiple myeloma is safe and synergies with pre-existing chronic graft versus host disease. A retrospective study from the CMWP EBMT

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CORRESPONDENCE

Daratumumab after allogeneic hematopoietic cell transplantation for multiple myeloma is safe and synergies with pre-existing chronic graft versus host disease. A retrospective study from the CMWP EBMT

- Dara post-alloHCT does not appear to increase the incidence of GVHD
- Superior PFS was seen in those with prior cGvHD
- Infections are common
- Extra-medullary disease progression is common

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As patients who have undergone alloHCT are often excluded from clinical trials, there is little published information on the use of Dara in this setting. Two multi-center retrospective series have been reported in the literature: a Spanish series of 25 myeloma patients including three plasma cell leukemias and an American series of 34 patients from three medical centers [1, 2]. We performed a retrospective study on 121 patients in the EBMT database to evaluate the safety and efficacy of Dara in the post-alloHCT setting. Patients with AL amyloidosis and plasma cell leukemia were excluded.

The primary safety parameter was the percentage of patients with an infection while on Dara (bacteremia, pneumonia, septic shock, urinary tract infection, CMV, and EBV reactivation). The primary efficacy endpoint was the disease control rate (DCR), defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), or stable disease (SD) within 26 weeks from the first administration of Dara [3]. Patients with missing best response data were considered progressive diseases.

Secondary safety endpoints were the incidences of acute and chronic graft-versus-host disease (aGvHD and cGvHD) after the start of Dara [4, 5]. Secondary efficacy endpoints were time to next treatment (TTNT), progression-free survival (PFS), overall survival (OS), and extramedullary disease (EMD).

The median age (range) at alloHCT was 55 (31–71) years.

Four patients have had three autoHCT before the alloHCT, 40 patients two autoHCT, 71 patients one autoHCT, and 6 patients no prior autoHCT preceding the alloHCT. Disease status pre-allo-HSCT was CR in 9%, VGPR in 35%, PR in 43%, SD/MR in 7%, and progressive disease in 6%.

All alloHCT were performed between 2004 and 2019 (median: 2014). AlloHCT was performed at a median of 34 (6–172) months after the diagnosis of myeloma. 14% of patients had upfront tandem auto-alloHCT. The stem cell source was peripheral blood in 88%, bone marrow in 9%, and cord blood in 2%. 37% of donors were matched related, 39% matched unrelated and 17% were mismatched. Conditioning regimen was reduced intensity (RIC) in 72% and myeloablative in 28%.

37% of patients had received at least one DLI infusion before receiving the first dose of Dara including 19% within the 6 months prior to starting Dara.

Before receiving the first dose of Dara, 25% of patients had presented with grade II to IV aGvHD (21% gr II, 3% gr III, and 1% gr IV) and 42% of patients had suffered from cGvHD (26% limited, 16% extensive). In 24% of patients, cGvHD was still present when Dara was started.

Six patients received Dara as post-alloHCT consolidation. All other patients received Dara following disease relapse. 48% of patients received Dara as their first salvage treatment. The first dose of Dara was given at a median of 30 (range: 1–173) months post-alloHCT. Dara were administered either alone ($n = 80$) or in combination with anti-myeloma directed therapy ($n = 41$) including lenalidomide ($n = 16$), bortezomib ($n = 13$), pomalidomide ($n = 9$), and carfilzomib ($n = 6$). The median duration of Dara administration was 5.9 months (95% CI: 4.1–8.2).

A total of 13% of patients received a median of two (range: 1–4) DLI infusions after the start of Dara. The median time to a DLI infusion was 8.9 months (range: 1.3–35) after starting Dara. Six patients were still on Dara at the time of DLI.

Among 116 patients with data available, bacteraemia was observed in 22.1%, (95% CI: 14.9–30.9) including 15% ≥grade 3, septic shock in 4.6%, (95% CI: 1.5–10.5), all ≥grade 3, pneumonia in 30.8%, (95% CI: 22.3–40.5), including 21% ≥grade 3, urinary tract infections in 7.3%, (95% CI: 3.2–14.0), CMV reactivation in 6.6%, (95% CI: 2.7–13.1) and EBV reactivation in 5.9%, (95% CI: 2.2–12.5).

Among the 102 patients with available data, the distribution of the best response to Dara was sCR/CR in 8%, VGPR in 10%, PR in 25%, SD/MR in 22% resulting in a DCR of 64% (54–73%). The best response was obtained at a median of 68 days after starting Dara.

EMD in soft tissues was observed in 15 % of patients after the start of Dara.

The median follow-up from the first dose of Dara was 26.8 months (95% CI: 22.3–31.1). The median TTNT was 18 months (95% CI: 9.2–the upper limit was not estimable). After starting

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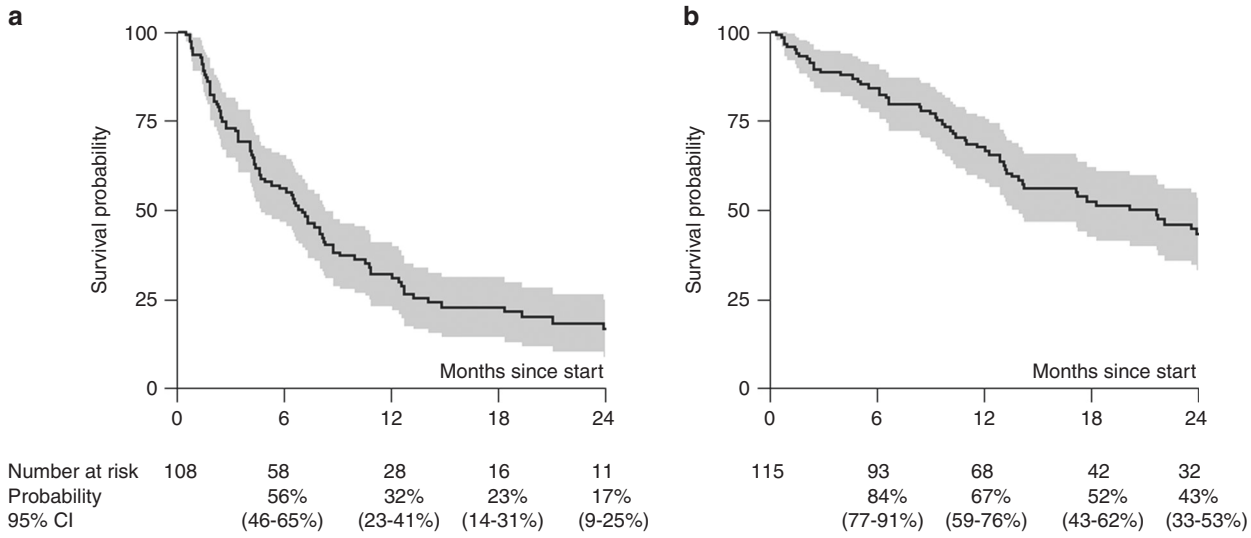

Fig. 1 Survival. a Progression-free survival (PFS) after the first administration of Dara. **b** Overall survival (OS) after the first administration of Dara.

Dara, the median PFS was 7.0 months (95% CI: 4.7–8.3) and the median OS 20.1 months (95% CI: 13.5–26.2) (Fig. 1). In multivariable analysis (MVA), there was a trend to a better PFS with RIC conditioning (HR 0.64, 95% CI: 0.39–1.05). Patients with pre-Dara cGvHD also had better PFS (HR 0.40, 95% CI: 0.24–0.66). Concerning OS, three factors were associated with a better OS in MVA: a longer interval between alloHCT and the subsequent relapse (HR 0.46, 95% CI: 0.27–0.79), RIC conditioning (HR 0.61, 95% CI: 0.35–1.08) and having had cGvHD prior to starting Dara (HR 0.55, 95% CI: 0.31–0.97).

The major causes of death were relapse/progression in 31%, infection in 19%, organ damage/failure in 6%, secondary malignancy/PTLD in 3%, GvHD in 1%, and others in 2%. Six of the 19 patients who died of infection had started Dara within the last 3 months.

In the first 100 days after starting Dara, aGvHD worsened by 2% (95% CI: 0–4%). The cumulative incidence of cGvHD within two years of starting on Dara was 4% (0–7%) including 3% with extensive cGvHD. Four out of five cases of cGvHD occurred within 6 months of starting treatment with Dara. All of them had had earlier cGvHD. One of the five cases of cGvHD occurred after DLI. None of them had received iMiDs.

This study of 121 patients with myeloma who were treated with Dara following an allogeneic stem cell transplant is the largest such analysis to date. It is the only study that has examined concomitant treatments including iMiDs and DLI, the incidence of infections, and the risk of extra-medullary relapse.

In terms of efficacy, assuming that allo-SCT is usually only performed in selected high-risk and even very high-risk myeloma patients, response rate (42%, 95% CI: 32–52%) and PFS (7.0 months, 95% CI: 4.7–8.3) appear encouraging. Interestingly, there was a trend to superior PFS in the RIC setting and in the context of pre-Dara cGvHD. We observed a worsening of aGvHD in only 2% and an incidence of cGvHD of 4% which is quite reassuring.

The proportions of infections observed in this study are high (22% rate of bacteremia, 5% septic shock, and 31% pneumonia) but similar to those observed under Dara or in alloSCT recipients [6–9].

A high incidence of EMD was observed but not superior to that previously reported in the allo setting [10, 11]. However, this observation supports the use of imaging, ideally PET-CT, on a regular basis in the post-allo setting.

In conclusion, this study provides support for the use of Dara in allogeneic transplant recipients. There was no significant impact on the induction of acute or chronic GvHD, no clear increase in the incidence of infections, and synergism with already existing cGVHD. The proportion of patients with extra-medullary disease appears to be similar to those reported in other myeloma alloHCT studies. In the context of such high-risk patients, the response and PFS rates appear encouraging.

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AUTHOR CONTRIBUTIONS

LV, SS, and MB designed the paper. LV, PC, JF, JP, SH, LR, MM, RT, JA van D, MH, PL, EF, CK, SD, JS, WS, TZ, and FM contributed to patient recruitment. All co-authors performed research. LG performed the statistical analysis. LV, LG, SS, MBL de W, PH, and IY-A wrote the paper. All authors approved the paper. LK did the data management.

COMPETING INTERESTS

Laure Vincent: consultancy: Janssen Cilag. Monique Minemma: consultancy: Alnylam, Janssen Cilag and Gilead, speakers Bureau: BMS and hospitality from Celgene. Raphael Teipel: honoraria: Janssen. Mathias Hanel: consultancy/advisory boards: Celgene, Amgen, Novartis, Takeda, GSK, honoraria: Celgene, Novartis, Takeda. Tsila Zuckerman: advisory board or speaker's bureau: AbbVie, Orgenesis Inc, BioSight Ltd, Cellect Biotechnology, Janssen, Novartis and Gilead Sciences. Stefan Schönland: honoraria: Janssen Cilag, Prothena, Takeda, Pfizer, research funding: Janssen Cilag, Sanofi, Prothena. Ibrahim Yakoub-Agha: honoraria: Celgene/BMS, Kite/Gilead, Janssen Cilag and Novartis. Meral Beksac: advisory board and speakers bureau: Amgen, Celgene, Janssen, Sanofi, Takeda, Oncopeptides. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

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