Upfront stem cell transplantation for newly diagnosed multiple myeloma with del(17p) and t(4;14) a study from the CMWP-EBMT

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ARTICLE

Upfront stem cell transplantation for newly diagnosed multiple myeloma with del(17p) and t(4;14): a study from the CMWP-EBMT

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Abstract

We analyzed newly diagnosed multiple myeloma patients with del(17p) and/or t(4;14) undergoing either upfront single autologous (auto), tandem autologous (auto-auto) or tandem autologous/reduced-intensity allogeneic (auto-allo) stem cell transplantation. 623 patients underwent either auto ($n = 446$), auto-auto ($n = 105$), or auto-allo ($n = 72$) between 2000 and 2015. 46% of patients had t(4;14), 45% had del(17p) while 9% were reported having both abnormalities. Five-year overall survival (OS) was 51% (95% confidence interval [CI], 45–58%) for single auto, 60% (95% CI, 49–72%) for auto-auto, and 67% (95% CI, 53–80%) for auto-allo ($p = 0.187$). Five-year progression-free survival (PFS) was 17% (95% CI, 12–22%), 33% (95% CI, 22–43%), and 34% (95% CI, 21–38%; $p = 0.048$). Five-year relapse rate was 82, 63, and 56%, while non-relapse mortality was 1, 4, and 10%. In multivariable analysis, in t(4;14) with single auto as reference, auto-auto (hazard ratio [HR], 0.44; $p = 0.007$) and auto-allo (HR, 0.45; $p = 0.018$) were associated with better PFS. In terms of t(4;14) and OS, auto-auto appeared to improve outcome compared with single auto (HR, 0.49; $p = 0.096$). In del(17p), outcome in PFS was similar between single auto and auto-auto, while auto-allo appeared to improve PFS (HR, 0.65; $p = 0.097$). No significant difference in OS was identified between the groups in patients with del(17p).

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Introduction

Multiple myeloma (MM) is a highly heterogeneous malignancy characterized by a variable disease course [1, 2]. Specific cytogenetic abnormalities confer poor outcomes in patients with MM, including t(4;14) and del(17p) [3, 4]. The International Myeloma Working Group (IMWG) molecular classification recommends testing for these abnormalities as standard for all patients with MM [5]. The ever evolving understanding of the molecular biology and the increased implementation of novel therapies within the MM treatment sequence has resulted in improved survival in recent decades, whereas the benefit did not seem to be equally distributed across subgroups [6]. Still, patients with high-risk cytogenetics perform worse than those at standard risk [4, 7]. High-dose chemotherapy plus autologous stem cell transplantation after initial induction therapy in combination with immunomodulatory drugs, proteasome inhibitors, alkylating agents, and corticosteroids improves outcome in newly diagnosed MM patients and is still considered standard of care for transplant-eligible patients [8]. More recently, the inclusion of immunotherapy using monoclonal antibodies such as daratumumab into front-line treatment approaches improved survival in patients eligible for transplantation [9].

Several approaches to further improve outcome after initial transplantation have been investigated such as a second transplant or consolidation with combination therapy [10, 11]. Comparative phase 3 trials have yielded conflicting results regarding the benefit of tandem transplantation, and none of the trials evaluated these different transplant approaches in specific cytogenetic subgroups [12–14]. Therefore, despite recent improvements in outcomes, current consensus indicates that t(4;14) and del(17p) still are associated with a poor outcome in MM patients, undergoing transplantation or nontransplant therapy. Here, we analyzed newly diagnosed MM patients with del(17p) and/or t(4;14) reported to the European Society for Blood and Marrow Transplantation (EBMT) registry undergoing either upfront single autologous (auto), tandem autologous (auto-auto) or tandem autologous/reduced-intensity allogeneic (auto-allo) stem cell transplantation.

Methods

Data selection

We included newly diagnosed MM patients with available data on cytogenetic analysis at time of diagnosis who received an upfront auto, auto-auto tandem transplant, or auto-allo tandem transplant between 2000 and 2015 and were reported to the EBMT registry. Tandem transplantation was defined as a second transplant within 6 months from first autologous transplantation, without a relapse in between. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing >600 transplant centers, mainly in Europe. Data are entered, managed, and maintained in a central database, while routine audits are performed to ensure accuracy of the data. Patients provide informed consent and the information is used in an anonymous way.

Statistics

The primary objectives of the study were overall survival (OS) and progression-free survival (PFS) within the first 5 years after the first autologous stem cell transplantation. Subsequently, events occurring after 60 months were artificially censored. OS was defined as the time between transplantation and death (from any cause) or last follow-up (for censored observations). PFS was defined as the time from transplantation to disease progression or death from any cause. The secondary end points were non-relapse mortality and cumulative incidence of relapse. Non-relapse mortality was defined as death without previous evidence of relapse or progression, with relapse or progression as competing events.

Survival probabilities of OS and PFS were estimated by the Kaplan–Meier method, and the log-rank test was used for univariate comparisons of subgroups. Median follow-up was calculated according to the reverse Kaplan–Meier method. Cumulative incidences of relapse and non-relapse mortality were analyzed together in a competing risks framework. Subgroup differences in cumulative incidences were analyzed using Gray's test. Landmark analyses starting at 6 months were used whenever transplantation strategies were compared, where patients were included if they were alive and relapse-free by 6 months after first autologous transplantation.

Multivariable analyses were used to investigate the effect of multiple risk factors on OS, PFS, and relapse. The most important effects estimated by the models were the interactions between transplantation strategy and cytogenetic abnormality (t(4;14) or del(17p)). The corresponding hazard ratios (HRs) were adjusted by the covariates age at first autologous transplant, categorized Karnofsky performance score (<90% and 90–100), disease stage at transplant (complete remission, less than complete remission), interval between diagnosis and first transplant and International Staging System (ISS). All estimates are reported with corresponding 95% confidence intervals (CI), and $p < 0.05$ was considered statistically significant (two-sided). All analyses were performed using the statistical software R version

3.4.3 (R Foundation for Statistical Computing, Vienna, Austria), using the packages survival, prodlim, and cmprsk.

Results

Patients characteristics of the total cohort

We identified 623 patients with newly diagnosed MM who underwent either auto ($n = 446$), auto-auto ($n = 105$), or auto-allo ($n = 72$) and who were reported to the EBMT database between 2000 and 2015. The median age of all patients was 59 years and the median interval between MM diagnosis and first transplant was 5.6 months. The median time between first and second transplant was 3.2 months for auto-auto and 3.6 months for auto-allo. 46% of patients had t(4;14), 45% had del(17p) while 9% were reported having both abnormalities. More than half of the included patients (56%) were male, had stage II according to ISS (58%), and presented with IgG type (53%). Allogeneic transplant was received from matched related donors in 39 patients (54%) and from matched unrelated donors in the remaining 33 patients (46%). The rest of the characteristics are summarized in Table 1.

The median follow-up of the total cohort was 58 months (53–63 months) with a 5-year OS of 49% (44–54%) and 5-year PFS of 20% (16–24%). Five-year relapse and non-relapse mortality rates were 77% (73–81%) and 3% (2–5%).

Outcome according to transplant strategy

Follow-up according to transplant strategy differed with a median of 56 months for single auto, 52 months for auto-auto, and 63 months for auto-allo. Figure 1 shows OS and PFS of the different transplant strategies after applying landmark estimates from month 6. Five-year OS was 51% (45–58%) for single auto, 60% (49–72%) for auto-auto, and 67% (53–80%) for auto-allo ($p = 0.187$). Five-year PFS was 17% (12–22%) for single auto, 33% (22–43%) for auto-auto, and 34% (21–38%) for auto-allo ($p = 0.048$). Five-year relapse rate was 82% (77–87%) for single auto, 63% (52–74%) for auto-auto, and 56% (42–70%; $p < 0.001$) for auto-allo while non-relapse mortality was higher for auto-allo (10%) compared with single auto (1%) and auto-auto (4%).

Outcome according to cytogenetics

No difference in 5-year OS was identified in univariate analysis showing 53% (46–60%) for t(4;14), 44% (37–51%) for del(17p), and 52% (37–67%) for patients with both abnormalities ($p = 0.463$). Furthermore, 5-year PFS was similar across the cytogenetic groups showing 20% (15–26%) for t(4;14), 20% (14–26%) for del(17p), and 16% (5–28%) for both abnormalities ($p = 0.179$). Five-year relapse rate and non-relapse mortality were also comparable between the cytogenetic groups showing corresponding rates of 76% (70–82%) and 3% (1–6%) for t(4;14), 77% (71–83%) and 3% (1–5%) for del(17p), and 78% (66–91%) and 6% (0–12%) for both ($p = 0.311$ and $p = 0.531$).

Table 1 Patient and transplant characteristics.

Characteristics	*N*	%
Age		
Median (range)	59 (25.6–76.7)	
Sex		
Female	277	44.5
Male	346	55.5
Transplant		
Auto	446	71.6
Auto-auto	105	16.9
Auto-allo	72	11.6
Cytogenetics		
del(17p)	279	44.8
t(4;14)	290	46.5
Both	54	8.7
ISS		
I	130	20.9
II	358	57.5
III	135	21.7
MM subtype		
IgA	159	25.6
IgG	331	53.4
Light chain	106	17.1
Non-secretory	16	2.6
Other Ig	8	1.3
Missing	3	
Karnofsky performance score		
<90%	159	29.0
90–100%	389	71.0
Number of high-risk cytogenetics		
1	480	77.0
≥2	143	23.0
Remission status at first transplant		
CR	109	17.8
No CR	503	82.2
Missing	11	
Induction regimen		
Bortezomib-based	431	69.2
Interval diagnosis-first transplant (months)		
Median (range)	5.6 (2.2–11.7)	

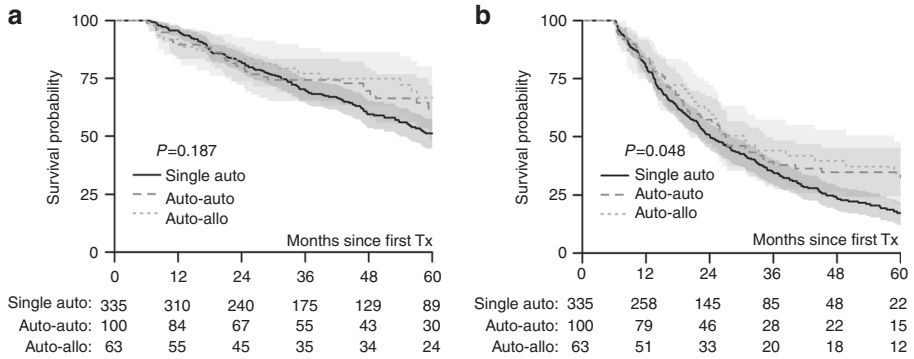

Fig. 1 Outcome according transplant strategy. Landmark overall (**a**) and progression-free survival (**b**) of different transplant strategies in multiple myeloma with t(4;14) or del(17p). Five-year overall survival was 51% (45–58%) for single auto, 60% (49–72%) for auto-auto, and 67% (53–80%) for auto-allo ($p = 0.187$). Five-year progression-free survival was 17% (12–22%) for single auto, 33% (22–43%) for auto-auto, and 34% (21–38%) for auto-allo ($p = 0.048$).

Outcome according to other patient- and transplant-related factors

Remission status did not seem to influence OS ($p = 0.452$). In contrast, PFS was significantly influenced by remission status ($p = 0.003$), as did incidence of relapse ($p < 0.001$). Five-year OS, PFS, and relapse of patients in complete remission before first transplant were 53%, 31%, and 63%, respectively. For patients with less than complete remission, outcome in OS, PFS, and relapse was 48, 18, and 79%. Categorization of induction as bortezomib-based compared with nonbortezomib-based regimens did not show difference in OS ($p = 0.220$) nor PFS ($p = 0.446$).

With regards to disease stage according to the ISS, higher stages appeared to show worse five-year OS ($p = 0.086$) being 58% for stage I, 48% for stage II, and 43% for stage III. In terms of PFS, higher ISS was significantly associated with worse PFS ($p = 0.041$) showing 23% for stage I, 21% for stage II, and 11% for stage III. Relapse also seemed to be different between disease stages ($p = 0.055$) showing 77% for stage I, 74% for stage II, and 87% for stage III.

A Karnofsky performance status of less than 90% appeared to show worse OS showing 44% compared with 53% of a performance status of 90–100%. However, no difference was identified for PFS and relapse. Female patients showed better 5-year PFS and lower relapse rates of 22 and 75% compared with 18 and 78% for male patients ($p = 0.044$ and $p = 0.105$). No association of sex and other outcome was identified.

Older age was associated with worse OS ($p = 0.026$). Especially patients at an age of more than 65 years showed worse PFS (8%) and high relapse rates (88%) compared with patients of less than 50 years (21 and 77%) or 50–65 years (21 and 75%).

Multivariable analysis

The multivariable evaluation of treatment effects (adjusted for age, Karnofsky performance status, time between diagnosis and first transplant, remission status at first transplant, and ISS stage) identified that the effect of auto-allo was dependent on the presence of del(17p) or t(4;14). Figures 2 and 3 depict landmarked survival curves for the different transplant strategies and within the different cytogenetic groups. The results of the final model on OS, PFS, and relapse are shown in Table 2.

Auto-auto showed similar outcomes compared with single auto in del(17p). In t(4;14), auto-auto was associated with improved PFS in compared with single auto (HR, 0.44; 95% CI, 0.24–0.80; $p = 0.007$), and appeared to improve OS (HR, 0.49; 0.21–1.14; $p = 0.096$). With regards to auto-allo in comparison with single auto, this approach appeared to be associated with better PFS (HR, 0.65; 95% CI, 0.40–1.08; $p = 0.097$) in del(17p) and was significantly associated with better PFS (HR, 0.45; 0.23–0.87; $p = 0.018$), while OS was comparable.

Discussion

Specific chromosomal abnormalities play a major role in MM prognostication, and previous studies suggested heterogeneous outcomes for patients carrying del(17p) or t(4;14) [15, 16]. However, currently existing and newly proposed cytogenetic risk classification often included a mix of therapies [4, 17], and outcome of different cytogenetic abnormalities may be affected by different treatment settings (e.g., transplant versus no transplant) [18, 19]. Collectively, the evolving treatment landscape in MM needs to identify subgroups that may benefit the most from specific therapy [20, 21].

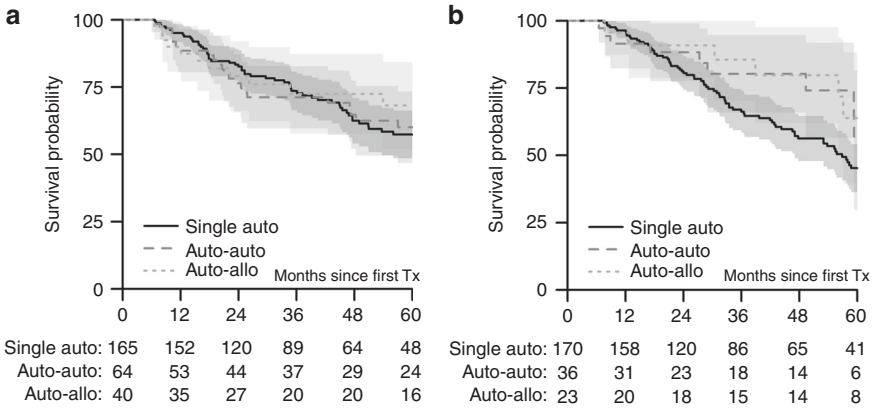

Fig. 2 Landmark overall survival of different transplant strategies in del(17p) (a) or t(4;14) (b). (**a**), overall survival in del(17p) was 56% (47–67%) for single auto, 58% (47–74%) for auto-auto, and 69% (50–81%) for auto-allo; (**b**), overall survival in t(4;14) was 46% (30–52) for single auto, 54% (26–77%) for auto-auto, and 63% (38-86%) for auto-allo. *P* values are not shown owing to the relatively low numbers in the auto-allo group.

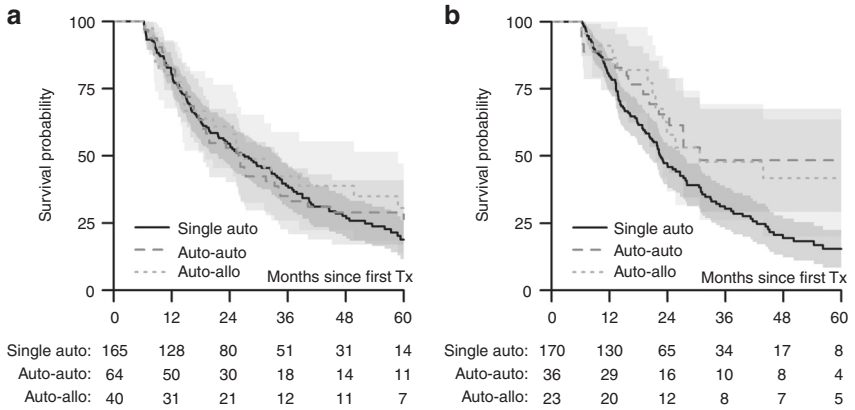

Fig. 3 Landmark progression-free survival of different transplant strategies in del(17p) (a) or t(4;14) (b). (**a**), progression-free survival in del(17) was 19% (11–26%) for single auto, 26% (18–35%) for auto-auto, and 29% (13–47%) for auto-allo; (**b**), progression-free survival in t(4;14) was 16% (8–23%) for single auto 49% (28–70) for auto-auto, and 43% (21–67) for auto-allo. *P* values are not shown owing to the relatively low numbers in the auto-allo group.

Therefore, we hypothesized that outcome of patients with del(17p) or t(4;14) may differ according to the upfront transplant strategy they were receiving. This analysis identified that upfront tandem transplantation, auto-auto or auto-allo, was associated with better PFS and reduced relapse in newly diagnosed MM patients with t(4;14) in comparison with single autologous transplantation. OS was at least comparable between the treatment and cytogenetic groups, while auto-auto appeared to show better OS in patients with t(4;14). Autologous-allogeneic stem cell transplant appeared to improve OS towards longer follow-up but showed higher non-relapse mortality within the first 6 months.

Using a tandem transplantation approach to increase dose intensity and to deepen response has been introduced to the MM treatment sequence >20 years ago, with several phase 3 trials demonstrating improvement in PFS, especially in patients who did not achieve complete remission after first autologous transplantation [12, 22]. At present, differing results and conclusions from two phase 3 trials (STAMINA and EMN02/HO95) evaluating the role of tandem transplantation cannot completely eliminate uncertainty regarding the question, which groups of patients benefit from this approach in an era of highly active induction regimens [13, 14]. A pooled analysis of phase 3 trials using induction with bortezomib, thalidomide, and dexamethasone (VTD) or doxorubicin, bortezomib, and dexamethasone with pre-specified randomization to single or tandem autologous transplantation reported improved outcome after a tandem approach [23]. In a high-risk group with high-risk cytogenetics and ISS stages II and III, median PFS was 35 months after tandem compared with 14 months with single

Table 2 Multivariable analysis on overall survival, progression-free survival, and relapse.

		OS		PFS		Relapse	
Covariate	Group	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Transplant*cytogenetic abnormality			0.079		0.0658		0.044
Single-auto: t(4;14)							
Auto-allo: t(4;14)		0.49 (0.2–1.25)	0.136	0.45 (0.23–0.87)	0.018	0.44 (0.23–0.85)	0.015
Auto-auto: t(4;14)		0.49 (0.21–1.14)	0.096	0.44 (0.24–0.8)	0.007	0.36 (0.19–0.69)	0.002
Single-auto: del(17)							
Auto-allo: del(17)		0.73 (0.34–1.58)	0.422	0.65 (0.4–1.08)	0.097	0.54 (0.32–0.93)	0.026
Auto-auto: del(17)		1.42 (0.84–2.4)	0.193	0.98 (0.65–1.46)	0.908	0.92 (0.61–1.39)	0.692
Cytogenetic abnormality	del(17p)						
	t(4;14)	1.27 (0.7–2.3)	0.428	1.31 (0.86–2.01)	0.212	1.26 (0.81–1.95)	0.312
Age (years)		1.18 (0.96–1.44)	0.109	0.98 (0.85–1.13)	0.755	0.96 (0.83–1.11)	0.559
Karnofsky score	90–100						
	<90	1.14 (0.8–1.63)	0.478	0.86 (0.66–1.13)	0.289	0.84 (0.64–1.11)	0.232
Stage at first transplant	CR						
	no CR	1.32 (0.83–2.1)	0.247	1.69 (1.2–2.37)	0.002	1.86 (1.3–2.65)	0.001
Interval diagnosis-first transplant (months)		1.04 (0.95–1.13)	0.417	1.02 (0.96–1.09)	0.559	1.02 (0.95–1.08)	0.641
ISS (diagnosis)	I						
	II	1.47 (0.94–2.3)	0.091	1.35 (0.99–1.85)	0.058	1.32 (0.96–1.8)	0.086
	III	1.78 (1.07–2.95)	0.026	1.62 (1.14–2.31)	0.008	1.64 (1.15–2.34)	0.007

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval, *auto* autologous, *allo* allogeneic, *ISS* International Scoring System.

transplantation. Together with these results and in view of the most recent updates from the STAMINA study showing long-term benefit for auto-auto in high-risk MM (Virtual ASCO 2020, abstract 8506), our analysis using real-world information may further strengthen the role of tandem autologous transplant in patients at high risk according to cytogenetics and disease [24].

With regards to different induction regimens, a meta-analysis of four European trials showed that tandem autologous transplant combined with bortezomib-based treatment may improve onset poor prognosis in patients carrying both t(4;14) and del(17p) [25]. More recently, a study using daratumumab plus VTD in comparison with VTD before and after autologous stem cell transplantation could show improved depth of response and PFS in standard-risk patients while no difference in outcome was observed in patients with high-risk cytogenetics [9]. In another recent study, the addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (D-VRD) in newly diagnosed transplant-eligible MM yielded significantly increased rates of minimal residual disease negativity. In high-risk MM, responses were not different, whereas PFS appeared to be improved, challenging the association of response and overall outcome in this subgroup [26]. In our analysis, the comparison of bortezomib-based and nonbortezomib-based induction did not show different outcomes. However, such categorizations in registry studies are retrospective and are prone to selection bias. For example, the use of certain induction modalities may be limited to European centers and differ from US centers. Taken together, the current standard of care may be bortezomib plus immunomodulatory drugs or chemotherapy, but risk-adapted therapy needs to be evaluated in future trials [7, 27].

Allogeneic stem cell transplantation has been proposed as a treatment for younger and fit patients at high risk, but data on the impact of this approach specifically in patients with cytogenetic abnormalities are scarce [28]. Our study provides some convincing albeit retrospective evidence that fit patients, especially those carrying t(4;14), may benefit the most from this approach. These results are further supported by a trial of 73 newly diagnosed patients, in which auto-allo transplantation yielded similar outcomes in patients with and without t(4;14) or del(17p) [29]. A recent prospective trial with long-term follow-up (median 91 months) comparing upfront auto-auto and auto-allo showed a median PFS of 22 months for auto-auto compared with 35 months for auto-allo [30]. In patients carrying both del(13q) and del(17p), outcome was significantly improved after auto-allo, but this subgroup analysis was limited by low number of patients (19 in auto-allo and 6 in auto-auto) [30]. Another recent but retrospective analysis in newly diagnosed MM at very high risk with extramedullary disease and high-risk cytogenetics

showed a trend towards better outcome using a tandem approach, either auto-auto or auto-allo, compared with single autologous transplantation. These results are also limited by the low number of patients receiving auto-allo transplantation ($n = 30$) [24]. As two other most recent reports demonstrated [31, 32], upfront tandem autologous transplantation may improve outcome (at least in PFS) in patients with newly diagnosed MM and upfront auto-allo approaches may provide long-term benefit for eligible high-risk patients.

Our study has several limitations. Only patients undergoing transplantation are reported to the EBMT registry and transplant-ineligible patients were not included [4], thus high-risk categorization may deviate compared with previous reports. However, the hypothesis of the study whether treatment may influence risk suggests the need for specific risk classifications for single and tandem transplant approaches, separately [17]. Another limitation of such a registry study is the lack of information of which maintenance therapy was applied. Multiple previous studies showed the benefit of maintenance therapy with lenalidomide or bortezomib after autologous transplant for MM patients with different risk profiles [33–35], while a recent trial introduced ixazomib as additional option for post-transplant maintenance therapy in patients with newly diagnosed MM prolonging PFS, even in high-risk cytogenetics [36]. With regards to the auto-allo approach, an association of different outcome and different conditioning regimen before allogeneic transplantation cannot be excluded [37].

Reporting on how cytogenetic information was assessed, unfortunately, is not usually done within the registry. Moreover, data on the mutational level, which were recently shown to provide predictive utility especially for high-risk classifications, were lacking [38]. Last, this analysis is of retrospective nature. Regression models, interaction as well as landmark analyses were used to control for between-group differences. However, adjustments cannot exclude all discrepancies within populations, resulting in selection bias. Thus, our results need to be interpreted in the context of these limitations.

In conclusion, we showed that upfront tandem transplantation, auto-auto or auto-allo, was associated with better PFS and reduced relapse in newly diagnosed MM patients with t(4;14) in comparison with single autologous transplantation. OS was at least comparable between the treatment and cytogenetic groups, while auto-auto appeared to improve OS in patients with t(4;14). In del(17p), auto-allo appeared to improve PFS, while no significant difference in OS was identified between the groups.

Author contributions NG and NK designed the study, analyzed data, interpreted results, and wrote the first draft of the manuscript; DJE, LCdW, and SI analyzed data and interpreted results; all authors contributed to writing the manuscript and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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