Comparison of tandem and single autologous stem cell transplantation in multiple myeloma: a retrospective propensity score-matching study

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Research Article

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Abstract

Background: Comparative data on the efficacy and safety of tandem or single autologous stem cell transplantation (ASCT) for patients with multiple myeloma (MM) in China are currently lacking. This study aimed to compare the clinical outcomes of tandem and single ASCT in real-world MM patients.

Methods: By utilizing a propensity score, we retrospectively analyzed the clinical data of 80 newly diagnosed MM patients who underwent ASCT in our center between November 2014 and November 2021, with 40 patients in each group receiving either single or tandem ASCT.

Results: The percentage of ≥ complete remission (CR) after the 1st and 2nd ASCT was 75% and 85% in the tandem ASCT group, compared to 77.5% in the single group. Since transplant, the median progression-free survival (PFS) was 33.2 months and 71.7 months for the single and tandem cohorts (p=0.0099). Median overall survival (OS) for the single and tandem groups was 39.3 months and 75.8 months (p=0.0515). The estimated 7-year PFS and OS since ASCT was 29.9% and 43.5% in the single group versus 47.5% and 54.4 % in the tandem group. Median PFS in patients with ISS II/III who underwent single ASCT was 29.8 months versus 66.4 months in the tandem group (p=0.008). Median OS since transplant was not reached in either group (p=0.1468). Among patients with high-risk cytogenetics, the median PFS was 23.2 months and 43.4 months for the single and tandem cohorts (p=0.0423), while the median OS was 37.1 months and not reached (p=0.0767). Among patients not achieving ≥ CR before ASCT, the median PFS was 24.3 months and not reached for the single and tandem cohorts (p=0.0187), while the median OS sincetransplant was not reached in either cohort (p=0.1631). No transplant-related mortality occurred in both cohorts. There were no significant differences between these two cohorts regarding both non-hematological and hematological toxicities.

Conclusions: Up-front tandem ASCT can deepen the depth of response and prolong the PFS of patients with MM, with a trend toward longer OS, particularly for patients with advanced ISS stages, high-risk cytogenetics, and no CR before transplant. Tandem ASCT may be tolerable for patients with MM.

Background

Up-front autologous stem cell transplantation (ASCT) has become the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM)[1, 2]. Tandem ASCT, known as two planned sequential ASCTs within 3–6 months, was developed to improve the overall survival (OS) in the conventional chemotherapy era, especially for patients who did not achieve a very good partial response (VGPR) after the first ASCT[2, 3]. In the novel agent era, however, controversial data exist regarding the efficacy of tandem ASCT. Several studies have confirmed the prolonged progression-free survival (PFS) and OS superiority of tandem ASCT, particularly for patients with high-risk cytogenetics[3–5]. By contrast, results from the STaMINA (BMT CTN 0702) trial showed no PFS and OS benefits from tandem ASCT over single ASCT[6]. Despite the conflicting roles, up-front tandem ASCT should be recommended to MM patients with high-risk cytogenetics[7, 8].

A previous study reported by our group demonstrated that up-front tandem ASCT could overcome the unfavorable prognosis of advanced International Staging System (ISS) stages and high-risk cytogenetics[9]. However, data regarding the comparison of tandem and single ASCT for MM patients in China are still lacking. Thus, we performed this retrospective matched-pair study to compare the clinical outcomes of single and tandem ASCTs in NDMM patients treated in our center to help bridge the knowledge gap in the real world.

Patients and Methods

Study design and patients

This retrospective propensity score-matching study was performed on transplant-eligible patients with NDMM treated in our center. We retrospectively reviewed our institution database of transplant-eligible patients with NDMM who underwent ASCT between November 2014 and November 2021, and who were followed up until February 2023. Tandem ASCT was defined as two planned sequential ASCTs within 3–6 months. Matching was performed for age, sex, subtype, β2-microglobulin, renal function, lactate dehydrogenase, cytogenetic risk, ISS stages, Revised-ISS stages, cytogenetics, induction regimens, disease status at the time of transplant, year of transplant, maintenance therapy regimen, and follow-up time (Fig. 1). All ethical considerations strictly followed the Declaration of Helsinki. Informed consent was obtained from all the patients for the study. This analysis was approved by the institutional ethics committee.

The presence of t (4;14), t (14; 20), t (14;16), amplification 1q, or del 17p via fluorescence in situ hybridization at the time of diagnosis was defined as high-risk cytogenetics. Response and disease progression were evaluated in accordance with the International Myeloma Working Group consensus response criteria. Post-ASCT response was assessed at a maximum of 90–100 days after transplant. Thereafter, patients were followed up every 2–3 months. PFS duration was calculated from the first transplant date until disease progression or death date. OS was defined as the time from the first transplant to death of any cause. Transplant-related mortality (TRM) was defined as death from any cause other than progression or relapse, occurring within 90 days and attributable to high-dose therapy. Absolute neutrophil count > 500/μL and platelet > 50.000/μL without transfusion support were defined as neutrophil and platelet engraftment, respectively.

Treatment regimens

The induction treatment included at least one novel agent, including proteasome inhibitors (PIs, bortezomib) and immunomodulators (IMiDs, lenalidomide). All the patients received a triplet induction regimen for 4–6 cycles before transplant. EA (etoposide 100 mg/m^2 qd d1–3 + cytarabine 0.5/m^2 q12h d1–3) regimen, followed by granulocyte colony-stimulating factor, was used as stem cell mobilization and collection procedure. High-dose melphalan (140–200 mg/m^2, depending on renal function) was administered as a conditioning regimen prior to ASCT. Two cycles of a previous induction regimen as

consolidation therapy was administered to patients with high-risk cytogenetics who did not achieve complete remission (CR) after their last transplant. All the patients received post-transplant maintenance treatment.

Statistical analysis

All statistical analyses were performed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Corp., Boston, USA). The SPSS software version 24.0 was used for propensity score matching and statistical analyses. Kaplan–Meier test was utilized to calculate PFS and OS duration, and long–rank tests with 95% confidence intervals (95% CI) were used to compare time-dependent outcome measures. Prognostic variables with an impact on OS and PFS were assessed using Cox regression analysis with the respective hazard ratios (HR). The p values < 0.05 were considered statistically significant.

Results

Patient- and treatment-related characteristics

By using a propensity score, we identified 80 patients, 40 of whom received either single or tandem ASCT (Fig. 1). The baseline characteristics of the patients who received single or tandem ASCT are described in Table 1. The two groups were evenly matched. According to cytogenetic features, the coexistence of amplification 1q and t (4:14) was more commonly observed in double/triple hit patients. With regard to induction treatment, most patients received bortezomib-based induction regimen prior to the year 2020, while bortezomib–lenalidomide–dexamethasone was the principal induction regimen from 2020. The median time between diagnosis and transplantation was 6.3 months (range: 4.3–10.9) and 6.2 months (range: 4.3–11.7) in the single and tandem transplant groups, respectively. Three (7.5%) patients in the single transplant group and four (10%) patients in the tandem group received consolidation therapy after the last transplant. The single agent lenalidomide was the most used maintenance treatment, followed by proteasome inhibitors (bortezomib or ixazomib). Two (5%) patients in the single transplant group and three (7.5%) patients in the tandem group received a combination of lenalidomide and bortezomib as maintenance therapy.

Table 1
Characteristics of patients with NDMM receiving single and tandem ASCT

Characteristics	Single cohort (n = 40)	Tandem cohort (n = 40)
Age (years), median (range)	55 (46–66)	53 (39–66)
Gender, n (%)		
Male	23 (57.7)	24 (60.0)
Female	17 (42.5)	16 (40.0)
Subtype, n (%)		
IgA	6 (15.0)	7 (17.5)
IgG	24 (60.0)	21 (52.5)
IgD	2 (5.0)	1 (2.5)
Light chain	8 (20.0)	11 (27.5)
ISS stage, n (%)		
	13 (32.5)	15 (37.5)
	14 (35.0)	12 (30.0)
	13 (32.5)	13 (32.5)
R-ISS stage, n (%)		
	10 (25.0)	10 (25.0)
	22 (55.0)	22 (55.0)
	8 (20.0)	8 (20.0)
Cytogenetics risk, n (%)		
Standard	15 (37.5)	14 (35.0)
High		
del (17p)	3 (7.5)	1 (2.5)
t (4;14)	/	1 (2.5)
t (14;16)	/	1 (2.5)
amplification (1q)	12 (30.0)	13 (32.5)
Double/Triple hit	10 (25.0)	10 (25.0)
Creatinine (μmol/L)		

Characteristics	Single cohort (n = 40)	Tandem cohort (n = 40)
Medium	104.5 (44–653)	102.6 (40–494)
>177, n (%)	4 (10.0)	5 (12.5)
Haemoglobin (g/L)		
Medium	97.7 (56–139)	96.8 (50–149)
<100, n (%)	20 (50.0)	19 (47.5)
Beta-2-MG (mg/L)		
Medium	5.4 (1.27–45.8)	5.2 (1.47–31.4)
>5.5, n (%)	11 (27.5)	10 (25.0)
LDH		
abnormal, n (%)	7 (17.5)	8 (20.0)
Induction regimens, n (%)		
PAD-based	20 (50.0)	22 (55.0)
VRD-based	16 (40.0)	14 (35.0)
VTD/VCD-based	4 (10.0)	4 (10.0)
Status at transplant, n (%)		
sCR/CR	24 (60.0)	20 (50.0)
VGPR	12 (30.0)	14 (35.0)
PR	4 (10.0)	6 (15.0)
Time diagnosis-first transplant (months), mean (range)	6.3 (4.3–10.9)	6.2 (4.3–11.7)
Time from first to second transplant (months), mean (range)	/	4.0 (3.1–5.3)
Consolidation therapy, n (%)	3 (7.5)	4 (10.0)
Maintenance treatment		
thalidomide	3 (7.5)	2 (5.0)
lenalidomide	28 (70.0)	26 (65.0)
bortezomib	4 (10.0)	4 (10.0)
ixazomib	3 (7.5)	5 (12.5)

Characteristics	Single cohort (n = 40)	Tandem cohort (n = 40)
lenalidomide + bortezomib	2 (5.0)	3 (7.5)

NDMM: Newly diagnosed multiple myeloma; ACST: autologous stem cell transplantation; LDH: lactate dehydrogenase; PAD: Bortezomib, liposome doxorubicin, and dexamethasone; VTD/VCD: Bortezomib, thalidomide/cyclophosphamide, and dexamethasone; VRD: Bortezomib, lenalidomide, and dexamethasone; sCR: Stringent complete response; CR: Complete response; VGPR: Very good partial response; PR: Partial response.

Response after ASCT

The response rate after ASCT is shown in Fig. 2A. After the last transplant, all the patients achieved VGPR or better in either arm. In particular, 31 patients (77.5%) in the single ASCT group achieved ≥ CR after ASCT, while 8 patients (20%) exhibited improved response after ASCT. In the tandem ASCT group, 30 patients (75%) achieved ≥ CR after the first ASCT, while 9 patients (22.5%) presented improved response after the first ASCT. In addition, 10 patients (25%) in the tandem ASCT cohort further improved their response after the second transplant, while 34 patients (85%) achieved ≥ CR after the second ASCT (Fig. 2A).

In the single transplant group, 6 (15%) patients, 3 of whom were double/triple hit with MM demonstrated early progression (< 12 months after transplantation): 3 patients between 3 months and 6 months, 2 patients between 7 months and 9 months, and 1 patient at 11.4 months. However, no patient in the tandem transplant group progressed within 1 year after transplantation.

Survival analysis

At data cutoff, with a median follow-up of 36.2 months (range: 12.9–116.4 months) from transplant, median PFS was 33.2 months (95% CI, 31.6–70.3) in the single group and 71.7 months (95% CI, 51.8–74.9) in the tandem group (p = 0.0099, Fig. 2B). Median OS from time of ASCT was 39.3 months (95% CI, 36.4–74.3) for the single cohort and 75.8 months (95% CI, 57.1–76.7) for the tandem cohort (p = 0.0515, Fig. 2C). The estimated 7-year PFS and OS from time of ASCT was 29.9% and 43.5% for patients in the single ASCT group versus 47.5% and 54.4% in the tandem group, respectively.

Outcomes according to different disease stages and cytogenetics

Furthermore, univariate analysis was performed to investigate the effect of single or tandem ASCT on the PFS and OS of patients with ISS Stage II/III at diagnosis and high-risk cytogenetics. Median PFS in patients with ISS II/III who underwent single ASCT was 29.8 months (95% CI, 16.3–32.9) versus 66.4 months (95% CI, 32.1–71.4) in the tandem group of patients (p = 0.008) (Fig. 3A). Median OS from time of transplant was not reached in either group (p = 0.1468) (Fig. 3B). According to cytogenetics, median

PFS in patients who exhibited high-risk cytogenetics was 23.2 months (95% CI, 10.3–44.1) and 43.4 months (95% CI, 23.9–55.3) in the single and tandem cohorts of patients, respectively (p = 0.0423) (Fig. 3C). Patients with high-risk cytogenetics who received single transplantation had a median OS of 37.1 months (95% CI, 16.1–50.9) versus not reached in the tandem group of patients (p = 0.0767) (Fig. 3D).

Pre-ASCT remission status has been proven to be a significant prognostic factor for predicting PFS and OS after ASCT. Therefore, we also evaluated the effect of single or tandem transplant on the PFS and OS of patients who did not achieve CR or better. A total of 16 (40%) and 20 patients (50%) in the single and tandem transplant groups did not obtain ≥ CR before ASCT, respectively. Since transplant, patients without ≥ CR had a longer PFS after tandem ASCT (median not reached) compared with patients who received single ASCT (median 24.3 months, 95% CI, 19.8–43.6, p = 0.0187, Fig. 4A). Median OS from time of transplant was not reached in either cohort (p = 0.1631) (Fig. 4B).

Multivariate analysis revealed that there were no significant differences in PFS and OS based on disease stages, cytogenetics, and pre-ASCT remission status between the two groups.

Transplant-related toxicity

This study also found low toxicity of tandem ASCT in real-world cases, with a Day 100 TRM of 0% in either cohort. No significant differences existed between the single and tandem cohorts regarding non-hematological toxicities. Oral mucositis, engraftment syndrome, and respiratory tract or intestinal infections were common but manageable complications. There were also no significant differences observed between these two cohorts in terms of hematological toxicities. In the single and tandem arms, median time until neutrophil engraftment was 11 days (range: 10–15) and 10.5 days (range: 9–14), while median time to platelet engraftment was 13 days (range: 10–17) and 13 days (range: 9–20), respectively. The median time of antibiotic therapy was 7 days in both arms (range: 5–10 and 6–11, respectively). For patients who received a second ASCT in the tandem arm, median times until neutrophil and platelet engraftment were 12 days (range: 10–25) and 17 days (range: 9–62), respectively. The median duration of antibiotic therapy was 8 days (range: 6–12) in the second transplant. One patient without exposure to lenalidomide developed a second primary malignancy (SPM), namely, acute lymphoblastic leukemia (ALL), 4.5 years after the second transplant.

Discussion

Tandem ASCT has been utilized to improve the depth of response and long-term outcomes in the chemotherapy era. However, different Phase 3 trials that explored the role of tandem transplant yielded mixed results, and the clinical value of tandem ASCT in patients with MM remained controversial in the novel agent era[10]. Furthermore, data regarding tandem ASCT for Chinese MM patients, particularly in terms of real-world nonspecific patients, remain limited. Previously, our single-center real-world study indicated that no significant difference in PFS and OS based on ISS stages and the cytogenetics risk of MM patients who underwent tandem ASCT, suggesting that high-risk patients with myeloma could benefit

from tandem transplant[9]. However, the lack of comparison with single ASCT was the major limitation of our previous study.

In the current retrospective matched-pair study, we compared single versus tandem ASCT as frontline treatment for NDMM in the real world. CR or better rates were significantly increased from first to second transplant in the tandem arm. We demonstrated superiority of tandem versus single ASCT with regard to PFS since transplant. A trend toward longer OS among patients who received tandem ASCT compared with those who received single ASCT was also observed. The probability of surviving 7 years from time of transplant was 54.4% in the tandem transplant group and 43.5% in the single transplant group. This survival benefit may be associated with deeper response after transplant. These results are consistent with those of other studies[4, 11]. An integrated analysis showed significantly improved PFS and 5-year OS in favor of tandem ASCT[3]. The randomized Phase III EMN02/HO95 study also demonstrated superiority of tandem versus single ASCT in terms of prolonged PFS and OS, with 25% increase in response depth and approximately 30% reduction in the risk of progression and death[5]. However, the lack of information on minimal residual disease (MRD) negativity is one limitation of this study, whereas MRD negativity is strongly associated with better PFS and OS.

A large body of evidence has proven that ISS stages and cytogenetics risk exert adverse prognostic effects on PFS and OS. In addition, several studies, including our previous study, have shown that MM patients with high risk will likely benefit the most from a tandem ASCT strategy. At present, it is recommended that tandem ASCT should be considered for MM patients with high-risk cytogenetics[7, 12], particularly for MM patients in China due to the lower availability of novel drugs. Here, our results suggested that tandem ASCT could improve clinical outcomes in patients with advanced ISS stages and high-risk cytogenetics, supporting our previous conclusion regarding the role of tandem ASCT. This real-world study may further strengthen the role of tandem ASCT in patients with high-risk disease characteristics and cytogenetics.

The Intergroupe Francophone du Myélome 2005-01 trial has revealed that the achievement of a high-quality response to induction therapy is associated with extended PFS after ASCT[13]. Moreover, another study showed that the achievement of CR by the time of ASCT was more important than that after ASCT, and the achievement of CR before ASCT was the sole prognostic factor for predicting improved OS[14]. In our study, more patients had no ≥ CR before ASCT in the tandem ASCT group than in the single group. Nevertheless, patients who underwent tandem ASCT presented improved PFS compared with single transplant among patients who did not achieve ≥ CR by the time of ASCT, suggesting that tandem ASCT could at least partially overcome the adverse prognosis of pre-ASCT remission status. Furthermore, a retrospective study indicated that response improvement after the 1st ASCT was a significant prognostic factor for survival benefit from tandem ASCT compared with single transplant in patients with MM[15]. Our analysis showed that the proportion of patients in ≥ CR was similar between the two cohorts after the 1st ASCT, and more patients achieved response improvement in the tandem group. Thus, the benefit

of tandem transplant in terms of counteracting negative effects of pre-ASCT remission status was likely linked to response improvement during transplant.

Apart from efficacy, another objective of the current study was to evaluate the safety and toxic effects of tandem ASCT. The results demonstrated the low toxicity of tandem ASCT in the real world, with a Day 100 TRM of 0%. Hematopoietic reconstitution was similar in the two groups. No significant differences regarding non-hematological toxicities were also found between the two cohorts. Common complications were oral mucositis, engraftment syndrome, and respiratory tract or intestinal infections, which were easily managed. SPM has become an increasingly relevant long-term risk in MM patients due to the significant improvement in survival[16]. The use of alkylator during ASCT and lenalidomide is associated with a potential increase in hematologic and some solid tumors. In the current study, one patient without exposure to lenalidomide developed ALL 4.5 years after the second transplant.

Several significant limitations of the current study included its retrospective nature and the relatively low number of patients included in the study. In addition, our study included the analysis of previously treated patients between the years 2014 and 2021. Therefore, significant variation in follow-up time is another limitation, and clinical outcome might have changed over follow-up time.

Conclusions

To the best of our knowledge, this study is the first reported analysis to compare single versus tandem ASCT among MM patients in China by using a relatively large sample. Compared with single ASCT, tandem ASCT is associated with higher ≥ CR rate and longer PFS, with a trend toward longer OS, particularly for MM patients with advanced ISS stages and high-risk cytogenetics. Moreover, similar to single ASCT, tandem ASCT may be tolerable for MM patients. However, the real-world evidence that we presented here has several limitations, and at present, an increasing number of novel drugs, including anti-CD38 monoclonal antibodies, bispecific antibodies, immunomodulatory agents, and newer generation proteasome inhibitors, have become available for treating NDMM patients. Therefore, conducting more studies concerning the efficacy and tolerability of tandem ASCT compared with single ASCT in the future is essential.

Abbreviations

ASCT	Autologous stem cell transplantation
MM	Multiple myeloma
NDMM	Newly diagnosed multiple myeloma
OS	Overall survival
VGPR	Very good partial response
PFS	Progression-free survival
ISS	International Staging System
TRM	Transplant-related mortality
IMiDs	Immunomodulators
CR	Complete remission
CI	Confidence intervals
HR	Hazard ratios
SPM	Second primary malignancy
ALL	acute lymphoblastic leukemia
MRD	Minimal residual disease

Declarations

Ethics approval and consent to participate

This present study was approved by the Ethics Committee of Fujian Medical University Union Hospital (IRB No.2021YF030-01). The Ethics Committee of Fujian Medical University Union Hospital waived the need for patient consent to participate in this study, as it involved retrospective data analysis and did not affect patient treatments.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study have been integrated into this published article.

Competing interests

The authors declare no competing interests. Furthermore, the funding bodies had no role in the study design, data collection, analysis, interpretation, or manuscript writing.

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Author contributions

Shun-Quan Wu, Xiao-Fan Li: data acquisition and analysis, statistical analysis, manuscript writing, manuscript revision, final approval of manuscript; Zong-Jian Qiu, Zhi-Juan Zhu: clinical management, data curation; Xian-Ling Chen, Ping Chen: clinical management and investigation, data analysis and interpretation; Rong Zhan: study design, clinical management; Nai-Nong Li: conceptualization, review the final version, supervision. All the authors read and approved the final manuscript.

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Figures

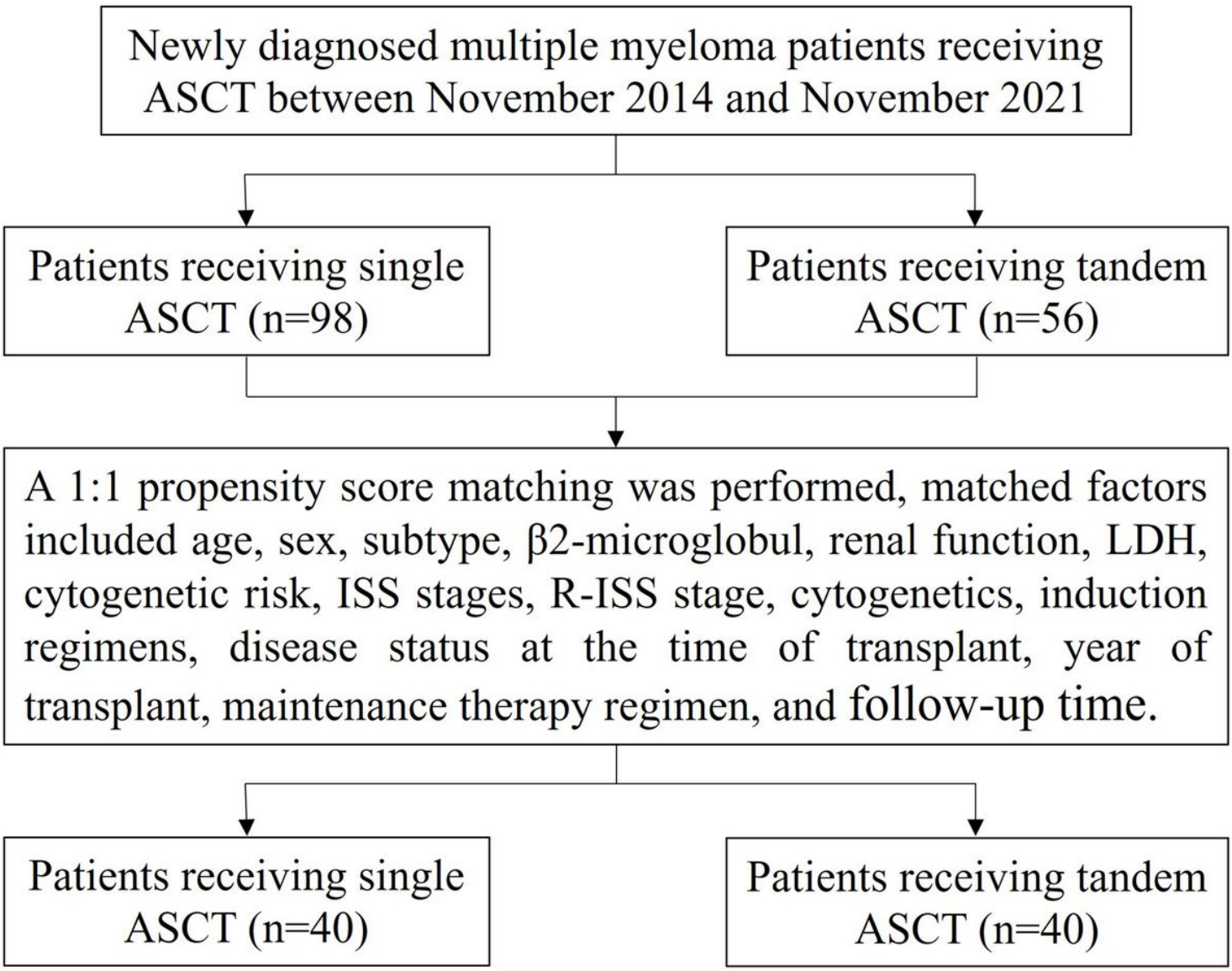

Figure 1

Flow chart of patient enrollment.

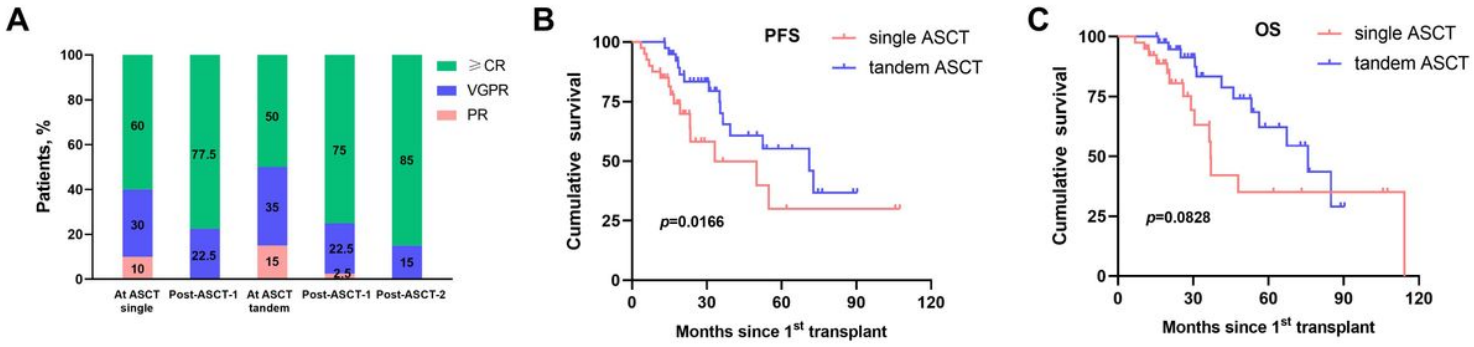

Figure 2

Response rate and cumulative incidences of PFS and OS in both groups of patients. (A) Response rate before and after ASCT. (B) PFS and (C) OS from transplant in patients undergoing single or tandem ASCT. PFS: Progression-free survival; OS: Overall survival; CR: complete remission; VGPR: very good partial response; PR: partial response.

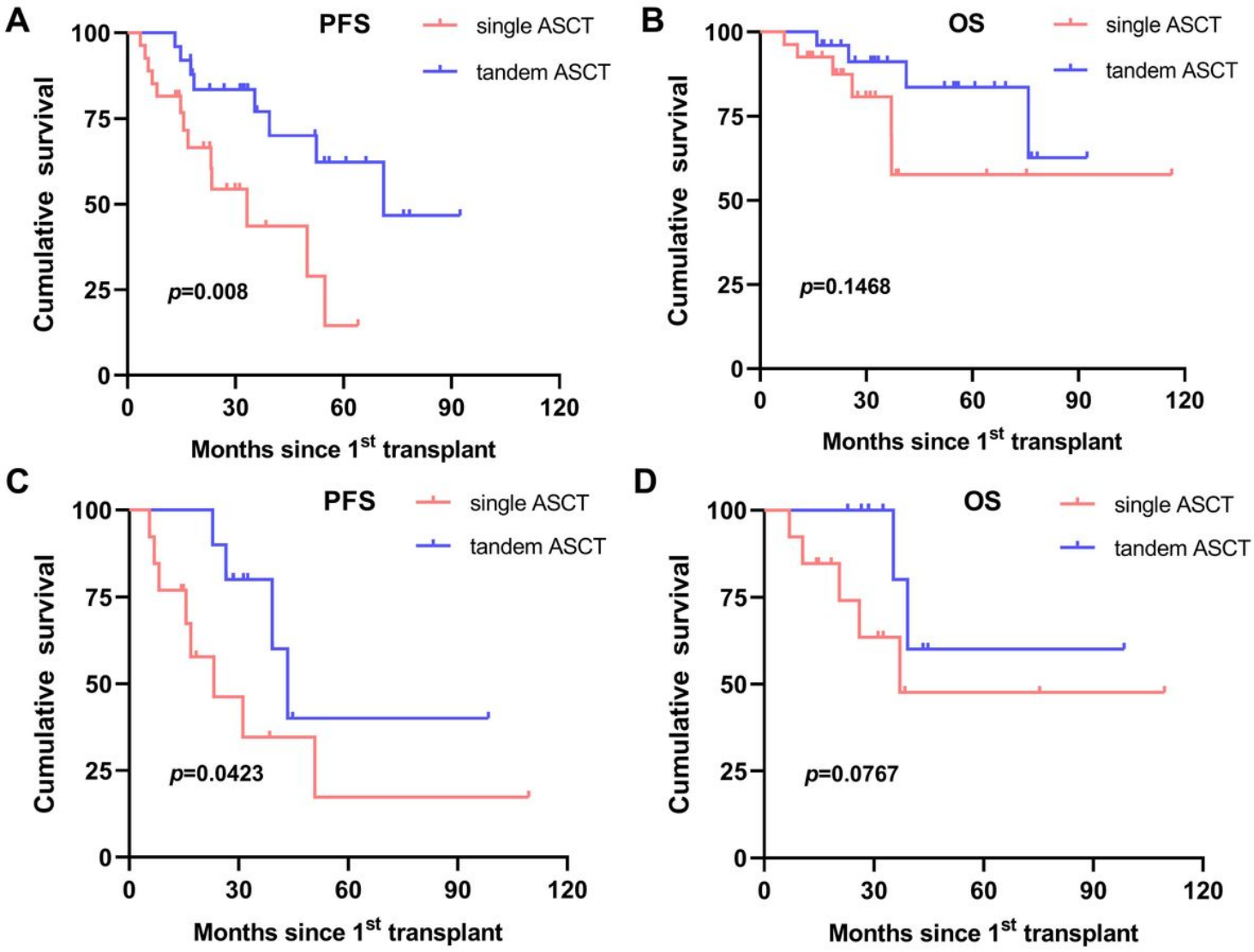

Figure 3

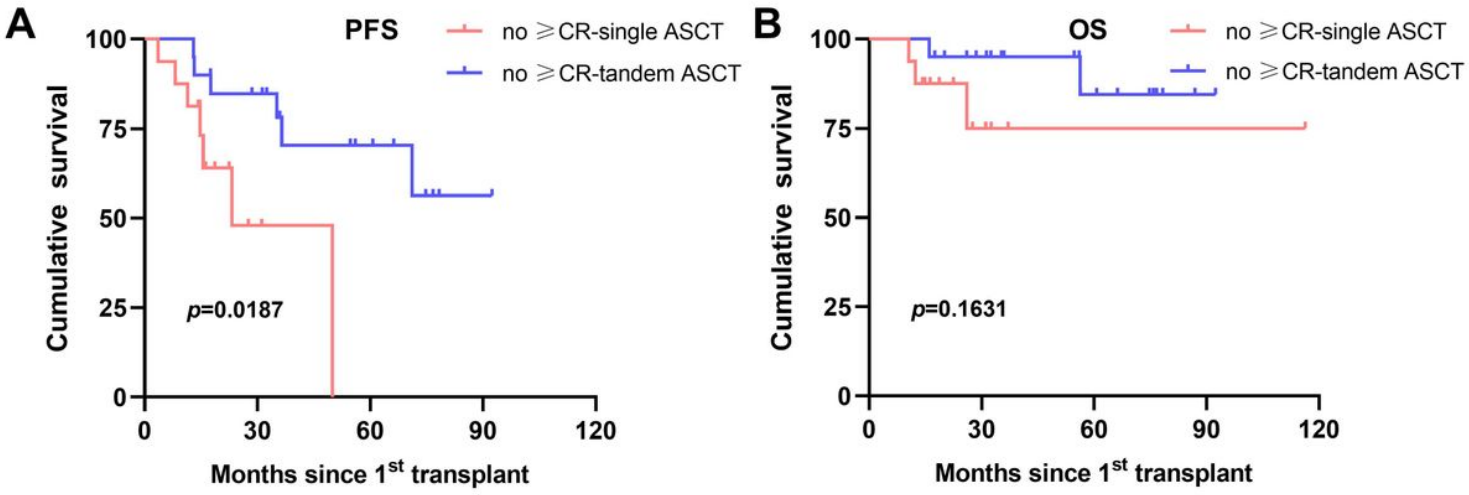

Figure 4

The cumulative incidences of PFS and OS for patients without ≥CR before ASCT. (A) PFS and (B) OS from transplant in patients without ≥CR before ASCTreceiving single or tandem transplant.