Consolidation With Second High Dose Therapy and Autologous Stem Cell Transplantation Is Associated With Improved Overall Survival in Patients With Multiple Myeloma in First Relapse

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Original Study

Consolidation With Second High Dose Therapy and Autologous Stem Cell Transplantation Is Associated With Improved Overall Survival in Patients With Multiple Myeloma in First Relapse

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Abstract

We aim to investigate the real-world outcomes of 237 patients with relapsed multiple myeloma, focusing on the role of repeated HDT/ASCT. Second HDT/ASCT was applied in 47% of patients. Significantly longer overall survival was observed in patients that received second HDT/ASCT, had no high-risk cytogenetics and had longer response duration after first HDT/ASCT. In the era of novel agents, second HDT/ASCT should still be considered as feasible and effective consolidative strategy.

Background: High dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) remains the preferred first line consolidation strategy for newly diagnosed multiple myeloma (MM). However, The role of HDT/ASCT in first relapse is uncertain in the context of novel therapies. This study evaluates real-world outcomes of MM patients in first relapse, focusing on the role of consolidative HDT/ASCT. **Patients and Methods:** This retrospective cohort study was conducted at a large tertiary referral center in Northern Netherlands. MM patients who received first-line HDT/ASCT and obtained a good response were included. The time to next treatment or death (TTNT-D 2) and overall survival (OS) were evaluated, while identifying prognostic factors. A landmark analysis was performed at 6 months, including only patients with a partial response (PR) or better after re-induction. **Results:** This study identified 237 patients potentially eligible for repeated HDT/ASCT of whom 111 (47%) underwent a second consolidative HDT/ASCT. The median follow-up is 40 months. Baseline characteristics were largely similar, though second HDT/ASCT was applied only after achieving PR or better. In the landmark analysis, absence of high-risk cytogenetics and good performance status were associated with longer TTNT-D 2. Consolidative second HDT/ASCT, absence of high-risk cytogenetics and longer first response duration were associated with longer OS. Transplantation-related mortality rate was < 1%. **Conclusion:** This study highlights the viability of second HDT/ASCT as treatment option for relapsed MM, particularly for patients with good responses to first-line HDT/ASCT. In the era of novel agents, second HDT/ASCT should be considered a feasible and effective consolidative strategy.

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Introduction

Treatment with induction therapy, high dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) and consolidation therapy is the preferred first line treatment for fit patients with multiple myeloma (MM).[1] Nowadays, quadruple over triple induction and consolidation therapy show the best survival outcomes. This is portrayed by the addition of daratumumab to bortezomib/thalidomide/dexamethasone in the Cassiopeia trial and to bortezomib/lenalidomide/dexamethasone in the Griffin and Perseus trials. The 4-year progression free survival (PFS) for quadruple therapy was around 68% in the Cassiopeia study, 87% in the Griffin study and 84% in the Perseus study.[2-4]

Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HDT/ASCT, high dose therapy and autologous stem cell transplantation; Imid, immunomodulatory drug; ISS, international staging system; MM, multiple myeloma; OS, overall survival; PFS, progression free survival; PI, proteasome inhibitor; PR, partial response; TTNT-D 1, time to next treatment or death 1; TTNT-D 2, time to next treatment or death 2; UMCG, university medical center groningen; VGPR, very good partial response.

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In the period 2014 to 2017 in the Netherlands, 63% of all patients under the age of 70 years were treated with consolidative HDT/ASCT.[5] Even after the introduction of more effective induction treatments, such as proteasome inhibitors (PIs) and immunomodulatory drugs (Imids), patients still benefit from HDT/ASCT consolidation. This benefit is portrayed in the IFM 2009, HOVON95 and FORTE studies, where patients treated with HDT/ASCT obtained a significantly longer PFS compared to patients treated without consolidative HDT/ASCT.[6-8]

Treatment for relapsed MM is rapidly evolving and includes the use of anti-CD38 monoclonal antibodies combined with either second generations PIs or Imids.[9] Again consolidative treatment with second HDT/ASCT might be beneficial when a reasonable remission duration has been obtained with first HDT/ASCT. EHA-ESMO guidelines recommend the use of second HDT/ASCT for relapsed MM in patients that have benefited for at least 18 months without lenalidomide maintenance treatment or at least 36 months with maintenance.[1] Literature on the use of second HDT/ASCT shows that it is feasible, but head-to-head comparisons with standard relapse treatments are limited. About 2 randomized controlled trials have been published which assessed the value of second HDT/ASCT. The Myeloma X trial[10] and the GMMG trial[11] both showed significantly longer progression free survival after second HDT/ASCT (PFS2) and overall survival (OS) compared to cyclophosphamide and lenalidomide-dexamethasone, respectively. Notably, in both older treatment modalities were used as comparison. With the recent improvements in outcomes of second line relapse treatment,[12-20] the question remains whether the use of a second HDT/ASCT is the preferred strategy in transplant-eligible patients with relapsed MM.

The aim of this study is to report the real-world outcomes of patients in first relapse after HDT/ASCT, including the use of second HDT/ASCT, from a large referral center in the Netherlands. Detailed data has been collected over an extended period of follow-up and includes patients treated during recent years in which more effective second line regimens are applied. Outcomes of patients potentially eligible for consolidative HDT/ASCT were analyzed and prognostic factors were identified.

Materials and Methods

Study design

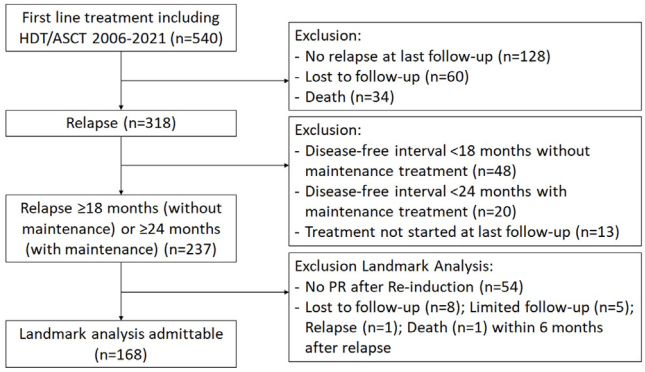
This is a retrospective cohort study analyzing patients with MM treated with consolidative HDT/ASCT in first line at the University Medical Center Groningen (UMCG). All newly diagnosed patients that received first HDT/ASCT from 2008 until 2021 ($n = 540$) were followed. All patients that experienced a first relapse with a disease-free interval of $\geq$ 18 months (without maintenance treatment) or $\geq$ 24 months (with maintenance treatment) were included (Figure 1). These intervals are based on historical local practices with second HDT/ASCT. Patients with plasma cell dyscrasia other than MM, including plasma cell leukemia, or treated with upfront tandem HDT/ASCT were not included. HDT always consisted of high dose melphalan, and all stem cells were collected before the first HDT/ASCT. Data have been collected from the local transplantation registry and individual patient records. Patients signed an informed consent at each transplant for use of coded patient data. The Institutional Review Board of the UMCG has approved this study.

Outcomes

The primary outcomes of this study are time to next treatment or death (TTNT-D) 2 and OS. Moreover, variables predictive of TTNT-D 2 and OS for all patients were investigated. For patients treated with second HDT/ASCT we also analyzed transplantation-related complications and made a comparison between TTNT-D 1 and TTNT-D 2. These are defined as the time, in months, between start of induction therapy in first, respectively, second line and the initiation of a new line of therapy or MM-related death, whichever came first. OS is defined as the time, in months, between the date of initiation of re-induction therapy and death. The depth of response is assessed according to the International Myeloma Working Group response criteria.[21]

The international staging system (ISS) stage is calculated at diagnosis.[22] High-risk cytogenetics is defined as the presence of del(17p), t(4;14) and/or t(14;16).[23] Refractory status is assessed at moment of relapse according to the International Myeloma Working Group criteria: Disease nonresponsive to therapy or

Figure 1 Patient flowchart.



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progression within 60 days of the last line of therapy.[24] This concerns bortezomib for PI-refractory and lenalidomide and thalidomide for Imid-refractory. For complications, the occurrence of infections/fever, mucositis, delirium, thrombosis, and Intensive Care Unit admissions in the first 100 days after transplantation are noted. The regeneration time is defined as the time in days between transplantation date and date of granulocytes higher than 0.5×10^9/L. Transplantation-related mortality is defined as death within a hundred days of transplantation without disease progression. Secondary malignancies are also noted.

Statistical analysis

Baseline characteristics are reported using descriptive statistics. TTNT-D and OS results are visualized using the Kaplan-Meier method. An initial cox regression analysis was performed to identify variables with a possible correlation with TTNT-D 2 or OS. Univariable analyses were performed for all variables with possible prognostic value (Table 1). Variables with a P-value $< .15$ were added to the multivariable model. Missing and unknown were added as categories to variables if date were missing completely at random. Backward selection was performed by removing the lowest contributing variable until a significance of $P < .05$ was reached for all variables. An additional landmark and sensitivity analysis was performed 6 months after the start of re-induction treatment and in patients with a partial response (PR) or better to correct for bias in the application of second HDT/ASCT for patients with early disease progression or poor response. The statistical analysis was performed in IBM SPSS (28) for windows.

Results

Baseline characteristics

Patient selection is depicted in Figure 1 and baseline characteristics are presented in Table 1. In our study cohort more than 95% of patients is Caucasian. Of the 540 patients treated with HDT/ASCT in first line, 237 patients received treatment for a relapse after a disease-free interval of at least 18 months. The median year of relapse is 2016. The median follow-up from start of re-induction treatment for these patients was 40 months (range 1-162 months). During follow-up, 65% of patients experienced a second relapse and 46% of patients died, of which > 90% related to MM or MM-treatment (Supplemental Table 1). The median age at first relapse was 63 years. High-risk cytogenetics were present in 15% of patients with available cytogenetics. The ISS stage at diagnosis was 33%, 41% and 26% for stage I, II and III, respectively. After the first HDT/ASCT, about one third of patients received post-transplant maintenance. The median TTNT-D 1 was 41 months. An Eastern Cooperative Oncology Group (ECOG)-performance status of 0 was present in 56% of patients at the time of relapse.

Treatment and response

Re-induction treatment consisted of triplet therapy for 61% of the patients. After re-induction, 77% obtained a PR or better. Second HDT/ASCT was applied in 111/237 (46%) of patients and the remaining 126/237 (54%) did not receive consolidative HDT/ASCT. Over time there was not a clear increase in the use of second HDT/ASCT (Supplemental Figure 1).

Baseline characteristics of the groups treated with and without HDT/ASCT are comparable, except for a slightly higher median age, more frequent use of anti-CD38 treatment and an inferior depth of response in the non HDT/ASCT group (Table 1). In the HDT/ASCT group 97% obtained a PR or better, while this was obtained by 60% in the non HDT/ASCT group. This indicates more use of second HDT/ASCT in younger patients that achieved a PR or better with re-induction treatment. Depth of response dynamics for the HDT/ASCT group is presented in Supplemental Figure 2 and Supplemental Table 2. In the HDT/ASCT group 48.5% of patients with ongoing response were treated with post-transplant maintenance, of which 88% with lenalidomide. In both patients treated with or without post second HDT/ASCT maintenance, the percentage treated with post-transplant maintenance after the first HDT/ASCT was about one third.

Time to next treatment or death

The median TTNT-D 2 in the entire cohort was 29 months (95% CI, 25-33 months). The 2-, 4- and 10-year TTNT-D 2 is 53%, 22% and 8%, respectively. At multivariable analysis high-risk cytogenetics (HR = 2,11; $P = .005$), a TTNT-D 1 < 4 years (HR = 1,89; $P = .001$), ECOG-performance score > 0 at re-induction (HR = 1,57; $P = .012$) and less than a PR (HR = 3,18; $P < .001$) after re-induction were associated with an inferior TTNT-D 2 (Figure 2; Supplemental Figure 3 and Supplemental Table 3).

Since application of second HDT/ASCT was mainly dependent on the response to re-induction treatment, we performed a landmark analysis to study the impact of consolidative HDT/ASCT among responding patients only. This only includes patients with a PR or better on re-induction treatment being alive without progression 6 months after initiation of re-induction treatment. Out of 237 patients, 168 were included in the landmark analysis, with 100 patients treated with and 68 without HDT/ASCT.

The median TTNT-D 2 of the patients included in the landmark analysis is 33 months (95% CI, 30-36 months). At multivariable analysis high-risk cytogenetics and a poor ECOG-performance status at re-induction showed significant prediction of an inferior TTNT-D 2. The median TTNT-D 2 in patients with absent and present high-risk cytogenetics is 35 months (95% CI, 30-40 months) and 23 months (95% CI, 11-35 months) (HR = 2,25; $P = .015$), respectively. The median TTNT-D 2 in patients with an ECOG-performance status at re-induction of 0 and > 0 was 36 months (95% CI, 26-46 months) and 29 months (95% CI, 20-38 months) (HR = 1,69; $P = .011$), respectively. (Figure 2; Supplemental Figure 3 and Supplemental Table 3)

In patients treated with second HDT/ASCT, the TTNT-D 2 is 35 months (95% CI, 31-39 months), while the TTNT-D 1 of this group with first HDT/ASCT was 44 months (95% CI, 40-48 months).

Overall survival

The median OS in the entire cohort was 60 months (95% CI, 49-71 months). The 2-, 4- and 10-year OS is 81%, 62% and 27%, respectively. In the multivariable analysis high-risk cytogenetics (HR = 2,02; $P = .028$), a shorter TTNT-D 1 (HR = 2,50; P

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Table 1 Baseline Characteristics and Treatment

	Full Cohort n (%)	HDT/ASCT Group n (%)	Non HDT/ASCT Group n (%)	*P*-Value
Total	237 (100)	111 (46.8)	126 (53.2)	
Age				< .01
At relapse, median (range), years	63 (34-76)	61 (34-73)	65 (46-76)	
Sex				.41
Male	145 (61.1)	71 (64.0)	74 (58.7)	
Cytogenetic risk				.37
Normal	135 (57.0)	61 (55.0)	74 (58.7)	
High	24 (10.1)	9 (8.1)	15 (11.9)	
Not available	78 (32.9)	41 (36.9)	37 (29.4)	
ISS				.99
1	61 (32.8)	29 (33.0)	32 (32.7)	
2	76 (40.9)	36 (40.9)	40 (40.8)	
3	49 (26.3)	23 (26.1)	26 (26.5)	
Missing	51 (21.5)	23 (20.7)	28 (22.2)	
Post-transplant maintenance				
After first HDT/ASCT	76 (32.1)	35 (31.5)	41 (32.5)	.87
TTNT-D 1				
Median (range), months	41 (18-168)	44 (19-145)	37.5 (18-168)	.31
≥ 4 years	83 (35.0)	43 (38.7)	40 (31.7)	.26
< 4 years	154 (65.0)	68 (61.3)	86 (68.3)	
Refractory status				
PI-refractory[a]	17 (7.2)	9 (8.1)	8 (6.3)	.60
Imid-refractory[b]	34 (14.4)	12 (10.8)	22 (17.5)	.15
PI- and Imid-refractory	4 (1.7)	1 (0.9)	3 (2.4)	
ECOG-performance status (at relapse)				.06
0	119 (56.4)	62 (62.6)	57 (50.9)	
1-3	92[c] (43.6)	37 (37.4)	55 (49.1)	
Missing	26 (11.0)	12 (10.8)	14 (11.1)	
Re-induction				.91
Triplet therapy	144 (61.0)	67 (60.9)	77 (61.1)	
Doublet therapy	92 (39.0)	43 (39.1)	49 (38.9)	
Re-induction				.02
PI-based[d]	86 (36.3)	52 (46.8)	34 (27.0)	
Imid-based[e]	93 (39.2)	42 (37.8)	51 (40.5)	
Anti-CD38-based[f]	44 (18.6)	15 (13,5)	29 (23.0)	
Others	14 (5.9)	2 (1,8)	12 (9.5)	

When data is missing for a variable, the percentages are based on the number of available patients.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; HDT/ASCT: high dose therapy and autologous stem cell transplantation; Imid: Immunomodulatory Drugs; ISS: International Staging System; n: number of patients; PI: proteasome inhibitor; TTNT-D 1: Time to next treatment or death 1.
[a]Patients refractory to bortezomib.
[b]Patients refractory to lenalidomide or thalidomide.
[c]Out of 92 patients, 75 patients have ECOG = 1; 15 patients have ECOG = 2; 2 patients have ECOG = 3.
[d]PI-based includes treatments based on bortezomib, carfilzomib or ixazomib.
[e]Imid-based includes treatments based on lenalidomide, pomalidomide or thalidomide.
[f]Anti-CD38-based includes treatments based on daratumumab or isatuximab.

< .001), no PR after re-induction (HR = 2,36; *P* < .001) and no consolidation with second HDT/ASCT (HR = 1,72; *P* = .018) (Figure 3A) showed a significant negative correlation with OS. Thus, patients treated with second HDT/ASCT showed better OS. (Figure 2; Supplemental Figure 4 and Supplemental Table 4).

The median OS of the patients included in the landmark analysis is 77 months (95% CI, 61-93 months). At multivariable analysis high-risk cytogenetics, a shorter TTNT-D 1 and no consolidation with second HDT/ASCT showed significant prediction of an inferior OS. The median OS in patients with absent and present high-risk cytogenetics is 89 months (95% CI, 77-101 months) and 46 months (95% CI, 23-69 months) (HR = 2,53; *P* = .021), respectively. The median OS in patients with a TTNT-D 1 of ≥ 4 years and < 4 years is not reached (NR) (95% CI, NR) and 69 months (95% CI, 54-84 months) (HR = 1,90; *P* = .041), respectively. The median OS in patients treated with and without HDT/ASCT was 80 months (95% CI, 58-102 months) and 63 months (95% CI, 38-88 months) (HR = 1,76; *P* = .020),

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Figure 2 Forest plot multivariable analyses: Hazard ratios and 95% Confidence intervals. Abbreviations: ECOG = eastern cooperative oncology group performance status; HDT/ASCT = high dose therapy and autologous stem cell transplantation; OS = overall survival; PR = partial response; TTNT-D = time to next treatment or death.

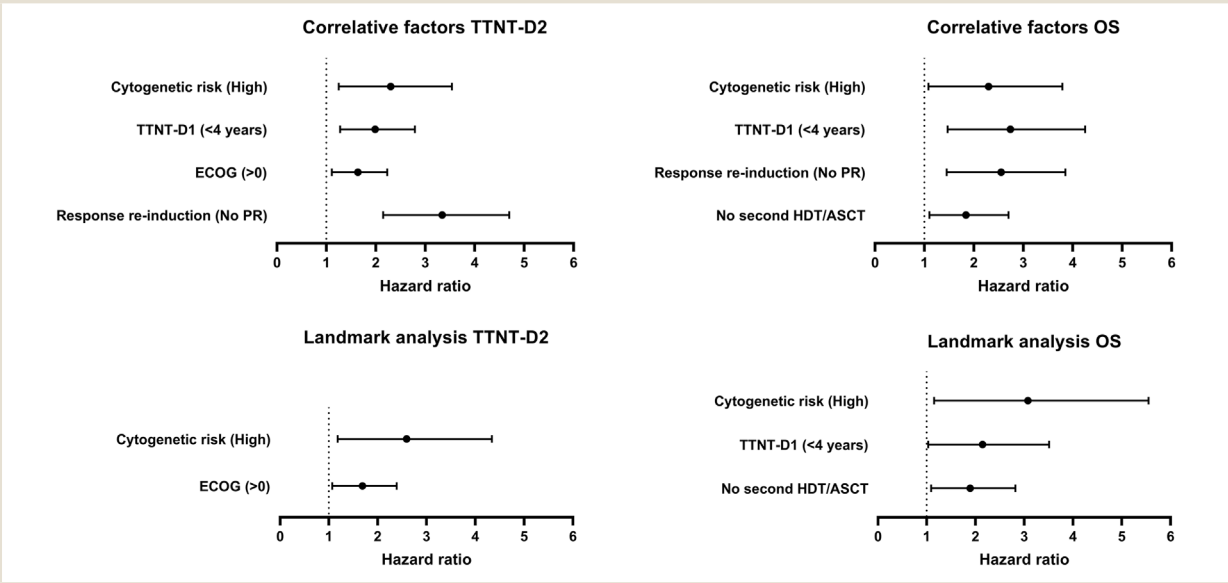
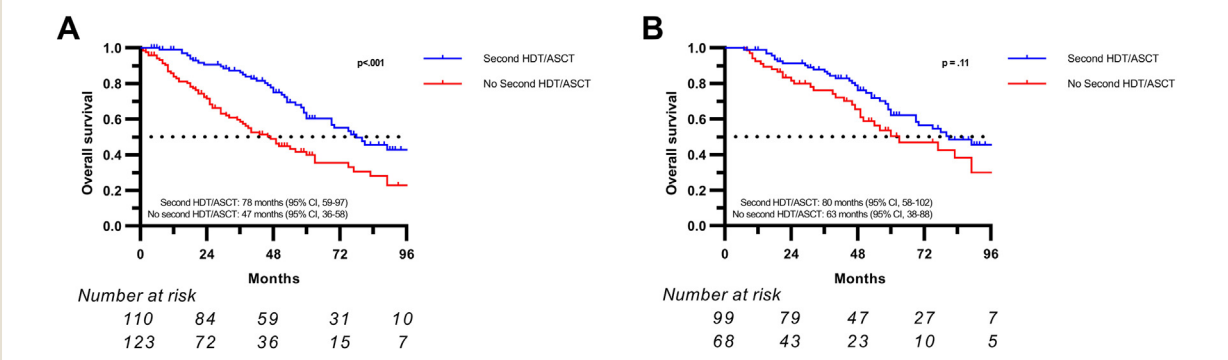


Figure 3 Survival HDT/ASCT. (A) Second HDT/ASCT Overall survival (B) Landmark analysis Second HDT/ASCT Overall survival. Abbreviation: HDT/ASCT = high dose therapy and autologous stem cell transplantation.



respectively (Figure 3B). (Figure 2; Supplemental Figure 4 and Supplemental Table 4)

In the second HDT/ASCT group there was 1 case (1%) of transplantation-related mortality after second HDT/ASCT and second primary malignancies did not have a higher incidence in patients treated with or without second HDT/ASCT (6 vs. 8 cases). (Supplemental Table 5).

Discussion

In this large population-based study, we analyzed the outcomes of MM patients in first relapse with a focus on the outcomes of patients in first relapse, including the impact of second consolidative HDT/ASCT. A significant improvement in OS and a nonsignificant improvement in the TTNT-D 2 were observed with consolidative second HDT/ASCT. We found that second HDT/ASCT was only applied as consolidative strategy in patients achieving a PR or better at re-induction treatment. In the landmark analysis, including only patients with a PR or better, we found that the use of second HDT/ASCT significantly correlates with a superior OS (median OS 80 vs. 63 months). Moreover, we confirmed well known baseline features, such as high-risk cytogenetics and response duration after first HDT/ASCT, to be predictive of TTNT-D 2 and OS. Failure to achieve a PR or better after re-induction was associated with worse TTNT-D 2 and OS.

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Our findings are particularly relevant due to the lack of recent randomized trials on the use of second HDT/ASCT in MM patients in first relapse. We selected all patients that relapsed after first HDT/ASCT and were theoretically considered eligible based on duration of response after first HDT/ASCT. Baseline characteristics for patients treated with and without second HDT/ASCT were similar, except for a slightly older age and different re-induction therapies for patients not receiving HDT/ASCT. Specifically, there was a higher use of anti-CD38-based regimens and lower use of PI-based regimens in patients not proceeding to HDT/ASCT consolidation. This difference might reflect the high tolerability and efficacy of anti-CD38 monoclonal antibodies that have influenced both patient and physician preferences to continue treatment instead of choosing for consolidative HDT/ASCT. However, the main factor that determined the use of second HDT/ASCT was the depth of response, in line with clinical practice where only patients with a PR or better are deemed eligible to proceed with HDT/ASCT. As other reason for continuing relapse treatment, 20 patients had insufficient stem cells left for a second HDT/ASCT.

After adjusting for biases due to nonresponse or early treatment failure at re-induction, the landmark analysis still demonstrated a significant OS benefit of 1,5 years for patients treated with a second transplantation. The median OS was 80 months compared to 63 months for patients not receiving second HDT/ASCT. Since second HDT/ASCT does not significantly improve TTNT-D 2, this cannot explain the OS benefit. The OS benefit could be due to a preserved susceptibility to applied re-induction therapies at time of first relapse. After a treatment-free interval, provided by second HDT/ASCT, these re-induction therapies could then be repeated at the time of second or later relapse. Additionally, the study population was treated during a period of many therapeutical advances. Although, about one third of patients in both groups received lenalidomide-based treatment at second relapse, exposure to novel regimens in later lines of therapy, may in part explain the OS benefit. Post-transplant maintenance after second HDT/ASCT was explored as possible cause for the OS benefit, but no OS differences were found between patients treated with and without post-transplant maintenance.

The median TTNT-D 2 of 35 months after second HDT/ASCT approaches the median TTNT-D 1 of 44 months after first HDT/ASCT, indicating that approximately 80% of the initial treatment response remains. Additionally, the rate of complications during first and second HDT/ASCT is comparable. The incidence of second primary malignancies is not higher compared to existing literature on the use of single HDT/ASCT, although the follow-up time might be too limited for definite conclusions. This all indicates that second HDT/ASCT is a viable, not overly toxic, treatment option for relapsed MM.

The median TTNT-D 2 of 35 months after second HDT/ASCT compares favorably to the outcomes of 2 randomized clinical trials examining the role of a second HDT/ASCT. While TTNT-D and PFS are not identical, they are closely related measures. The Myeloma X trial[10] reported a median PFS of 19 months and the GMMG trial[11] a median PFS of 20.7 months. Recently, 2 studies published retrospective data on PFS2 and OS after second HDT/ASCT for relapsed MM. The European Society for Blood and Marrow Transplantation[25] reported a 2-year PFS2 of 39% and a 4-year OS of 52% among 305 patients. In contrast, the Center for International Blood and Marrow Transplant Research[26] reported a 3-years PFS2 of 13% and a 3-year OS of 68% among a cohort of 975 patients. An observed 2-year TTNT-D 2 of 63% and 4-year OS of 75% in the second HDT/ASCT group is substantially better. This improvement may be explained by the use of more potent re-induction treatments in recent years.

When compared to currently applied second line of therapies, the Pollux trial[12] showed a median PFS of 44 months with daratumumab, lenalidomide and dexamethasone for patients who had not previously received lenalidomide. The TTNT-D 2 in our second HDT/ASCT cohort matches with findings of the Candor[13] and Ikema[14] trials, in which daratumumab or isatuximab were combined with carfilzomib and dexamethasone (29 and 36 months median PFS, respectively). Of note, these studies included patients already treated with multiple lines of therapy, limiting direct comparability. However, these effective therapies can also be used as re-induction treatment before second HDT/ASCT. This approach offers several advantages over continuing relapse treatment, including the likelihood that patients remain susceptible to these therapies at a later relapse, potentially leading to a longer TTNT-D 3 and OS. Additionally, the treatment-free interval might be increased, and treatment costs reduced, being relevant outcomes for patients and society.

An important limitation of our study is its retrospective nature with patients included over an extended period in which various re-induction regimens have been used, also leading to a considerable amount of missing data. Next, we could only partly identify factors that influenced HDT/ASCT treatment decision making at the time of relapse. However, this is the largest single center study reporting on the outcomes of second HDT/ASCT for relapsed MM, where 61% of patients were treated with triple re-induction therapy and novel re-induction treatment options, such as carfilzomib and daratumumab, were administered to 29% of patients. Furthermore, by investigating the whole transplant eligible population and accounting for potential confounders, our findings offer a more comprehensive perspective on the efficacy of second HDT/ASCT. This increases the applicability and relevance to current clinical decision making.

Based on these findings and previous reports on the use of second HDT/ASCT, it would be most appropriate to conduct randomized controlled trials comparing second HDT/ASCT head-to-head with other treatment options, such as anti-CD38-carfilzomib-dexamethasone triplets and emerging modalities like bi-specific antibodies and CAR-T cell therapy.[27-29] Importantly HDT/ASCT allows for a treatment free interval and has important financial benefits compared to the continuation of relapse treatment. Therefore, a comprehensive head-to-head analysis, including treatment cost and quality of life outcomes, is essential for identifying potential gains in quality-adjusted life years and assessing cost-effectiveness.

Conclusion

In conclusion, our retrospective study demonstrates that second HDT/ASCT is an effective treatment option for patients with relapsed MM associated with a significant OS benefit and a trend

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for longer TTNT-D2, without being overly toxic. Especially in patients that experienced limited toxicity during first transplant and have a disease-free interval of at least 24 months after the first HDT/ASCT, second HDT/ASCT is a viable treatment option. This treatment approach could provide a long treatment-free interval with additional financial and quality of life benefits. Further head-to-head comparisons with highly effective novel treatment options including bispecific antibodies and CAR-T cells are warranted.

Clinical practice points

- In the era of novel agents, second HDT/ASCT should be considered as consolidative strategy in relapsed multiple myeloma as it is associated with favorable overall survival and low toxicity.
- High-risk cytogenetics, a shorter initial response duration, poor performance status and failure to achieve a partial response or better with re-induction are associated with a shorter time to next treatment and/or overall survival in relapsed multiple myeloma.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Koen M. Klomberg: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Miriam Gelderloos:** Data curation, Conceptualization. **Hilde A.M. Kooistra:** Writing – review & editing, Validation, Methodology, Formal analysis. **Marcel Nijland:** Writing – review & editing, Formal analysis. **Gerwin A. Huls:** Writing – review & editing, Supervision, Conceptualization. **Wilfried W.H. Roeloffzen:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Wouter J. Plattel:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

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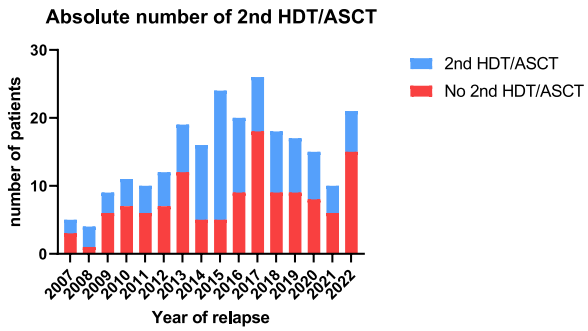
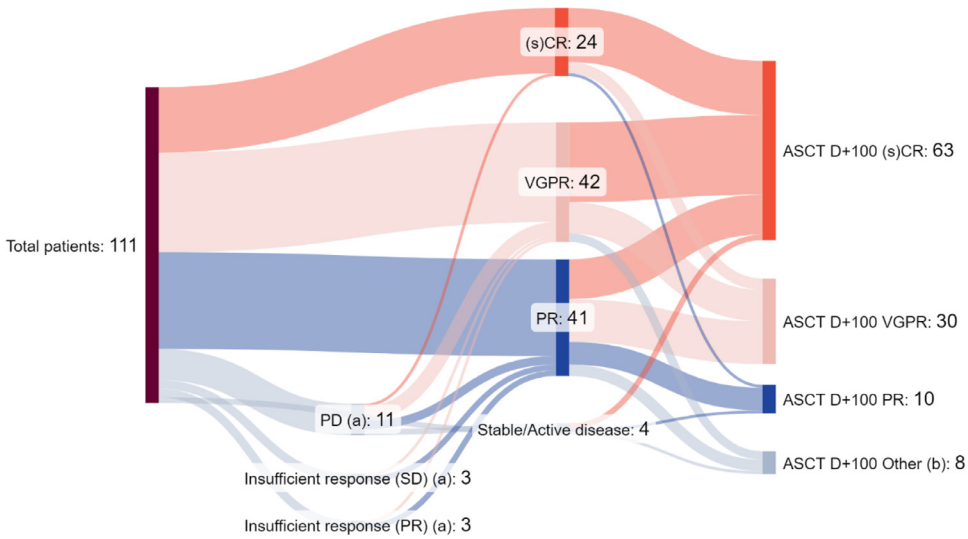
Supplemental material

Supplemental Figure 1 . Absolute number of patients treated with second HDT/ASCT per year of relapse. Total number of patients per year of relapse after first HDT/ASCT and share treated with and without second HDT/ASCT.



Supplemental Figure 2 Sankey Diagram. Depth of response before and after second HDT/ASCT. Sankey diagram showing the depth of response dynamics for patients treated with second HDT/ASCT. The presented values are the number of patients within each category.
Abbreviations: ASCT *D*+100: Day 100 after transplantation; (s)CR: Complete response or better; HDT/ASCT: high dose therapy and autologous stem cell transplantation; PR: Partial response; PD: Progressive disease; SD: Stable disease; VGPR: Very good partial response.
a: 17 patients had either progressive disease or insufficient response after the first re-induction therapy and switched to another re-induction treatment.
b: 'ASCT *D*+100 Other' consisted of 6 unknown cases, 1 case of stable disease and 1 case of not reached due to Transplantation-related mortality.



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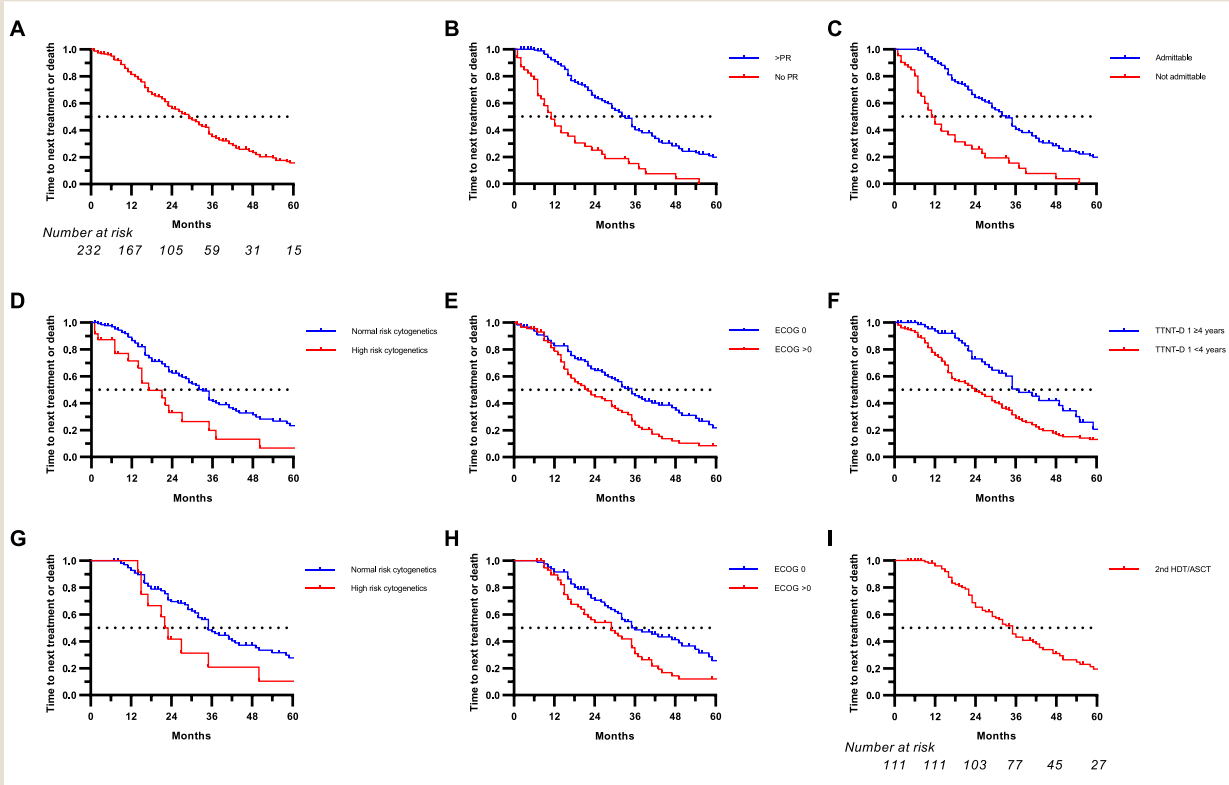
Supplemental Figure 3 Time to next treatment or death. (A) Total: The median TTNT-D is 29 months (95% CI, 25-33 months). (B) Response re-induction: The median TTNT-D for PR or better is 32 months (95% CI, 29-35 months) and for no PR is 10 months (95% CI, 7-13 months)(HR = 3,18; $P < .001$). (C) Landmark exclusions: The median TTNT-D for inclusion in the landmark analysis is 33 months (95% CI, 30-36 months) and for exclusion in the landmark analysis is 11 months (95% CI, 8-14)(HR = 3,41; $P < .001$; only univariable analysis). (D) cytogenetic risk: The median TTNT-D for absent high-risk cytogenetics is 35 months (95% CI, 31-39 months) and for present high-risk cytogenetics is 17 months (95% CI, 5-29 months)(HR = 2,11; $P = .005$). (E) ECOG-performance status at re-induction: The median TTNT-D for an ECOG of 0 is 35 months (95% CI, 30-40 months) and for an ECOG of > 0 is 22 months (95% CI, 16-28 months)(HR = 1,57; $P = .012$). (F) TTNT-D 1 groups: The median TTNT-D for a TTNT-D1 of ≥ 4 years is 35 months (95% CI, 27-43 months) and for a TTNT-D1 of < 4 years is 24 months (95% CI, 18-30 months)(HR = 1,89; $P = .001$). (G) Landmark analysis cytogenetic risk: The median TTNT-D for absent high-risk cytogenetics is 35 months (95% CI, 30-40 months) and for present high-risk cytogenetics is 23 months (95% CI, 11-35 months)(HR = 2,25; $P = .015$). (H) Landmark analysis ECOG-performance status at re-induction: The median TTNT-D for an ECOG of 0 is 36 months (95% CI, 26-46 months) and for an ECOG of > 0 is 29 months (95% CI, 20-38 months)(HR = 1,69; $P = .011$). (I) The median TTNT-D for patients treated with second HDT/ASCT: Median TTNT-D1 for first HDT/ASCT is 44 months (95% CI, 40-48 months) and Median TTNT-D2 for second HDT/ASCT is 35 months (95% CI, 31-39 months). Abbreviations: ECOG: Eastern Cooperative Oncology Group; PR: Partial response; TTNT-D 1: Time to next treatment or death 1.



Supplemental Table 1 Causes of Death

	Full Cohort n (%)	HDT/ASCT Group n (%)	Non HDT/ASCT Group n (%)
Total	237 (100)	111 (46.8)	126 (53.2)
Total Deaths	109 (46.0)	44 (39.6)	65 (51.6)
Progressive Multiple myeloma	76 (69.7)	29 (65.9)	47 (72.3)
Treatment-related	14 (12.8)	5 (11.4)	9 (13.8)
Second malignancy	6 (5.5)	2 (4.5)	4 (6.2)
Other/Unknown	13 (11.9)	8 (18.2)	5 (7.6)

The percentages of the exact causes of death are based on the total number of deaths
Abbreviations: HDT/ASCT: high dose therapy and autologous stem cell transplantation; n: number of patients.

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Supplemental Table 2 Depth of Response First and Second Line

	After (Re-)Induction			ASCT *D*+100	
	First HDT/ASCT n (%)	*Second HDT/ASCT n (%)*	*Non Second HDT/ASCT [a] n (%)*	*First HDT/ASCT n (%)*	*Second HDT/ASCT n (%)*
Total	111 (100)	111 (100)	126 (100)	111 (100)	110 (100)
CR or better	32 (28.8)	24 (21.6)	30 (28.8)	63 (57.3)	63 (60.6)
VGPR	37 (33.3)	44 (39.6)	22 (21.2)	35 (31.8)	30 (28.8)
PR	42 (37.8)	40 (36.0)	23 (22.1)	12 (10.9)	10 (9.6)
SD	0 (0.0)	2 (1.8)	15 (14.4)	0 (0.0)	1 (1.0)
PD	0 (0.0)	1 (0.9)	14 (13.5)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	22 (17.5)	1 (0.9)	7 (6.3)

When data is missing for a variable, the percentages are based on the number of available patients.
Abbreviations: ASCT *D*+100: Day 100 after transplantation; CR: Complete response; HDT/ASCT: high dose therapy and autologous stem cell transplantation; n: number of patients; PR: Partial response; PD: Progressive disease; SD: Stable disease; VGPR: Very good partial response.
a: This concerns the best recorded response with Re-induction

Supplemental Table 3 Multivariable Analyses Time to Next Treatment or Death

	Correlating Factors TTNT-D 2				Landmark Analysis TTNT-D 2			
	n	*HR*	*95% CI*	*P-Value*	*n*	*HR*	*95% CI*	*P-Value*
Cytogenetic Risk								
Normal	135	1			102	1		
High	24	2,11	1,25-3,54	.01	12	2,26	1,18-4,34	.02
ECOG-Performance Status at Re-Induction								
0	119	1			86	1		
> 0	92	1,57	1,11-2,23	.01	60	1,60	1,07-2,39	.01
TTNT-D 1 Groups								
≥ 4 years	83	1						N.S.
< 4 years	154	1,89	1,28-2,79	< .01				
Response Re-Induction								
PR or better	54	1						N.A.
No PR	54	3,18	2,15-4,70	< .01				

Abbreviations: CI: Confidence interval; HDT/ASCT: high dose therapy and autologous stem cell transplantation; HR: Hazard ratio; n: number of patients; N.A.: Not Applicable; N.S.: Not Significant; PR: Partial response; TTNT-D 1: Time to next treatment or death 1; TTNT-D 2: Time to next treatment or death 2.

Supplemental Table 4 Multivariable Analysis Overall Survival

	Correlating Factors OS				Landmark Analysis OS			
	n	*HR*	*95% CI*	*P-Value*	*n*	*HR*	*95% CI*	*P-Value*
Cytogenetic Risk								
Normal	134	1			101	1		
High	24	2,02	1,08-3,79	.03	12	2,53	1,15-5,55	.02
TTNT-D 1 Groups								
≥ 4 years	82	1			62	1		
< 4 years	154	2,50	1,47-4,25	< .01	105	1,90	1,03-3,51	.02
Second HDT/ASCT								
Yes	110	1			99	1		
No	126	1,72	1,10-2,70	.02	68	1,76	1,09-2,82	.02
Response Re-Induction								
PR or better	182	1						N.A.
No PR	54	2,36	1,45-3,85	< .01				

Abbreviations: CI: Confidence interval; HDT/ASCT: high dose therapy and autologous stem cell transplantation; HR: Hazard ratio; n: number of patients; N.A.: Not Applicable; OS: Overall survival; PR: Partial response; TTNT-D 1: Time to next treatment or death 1.

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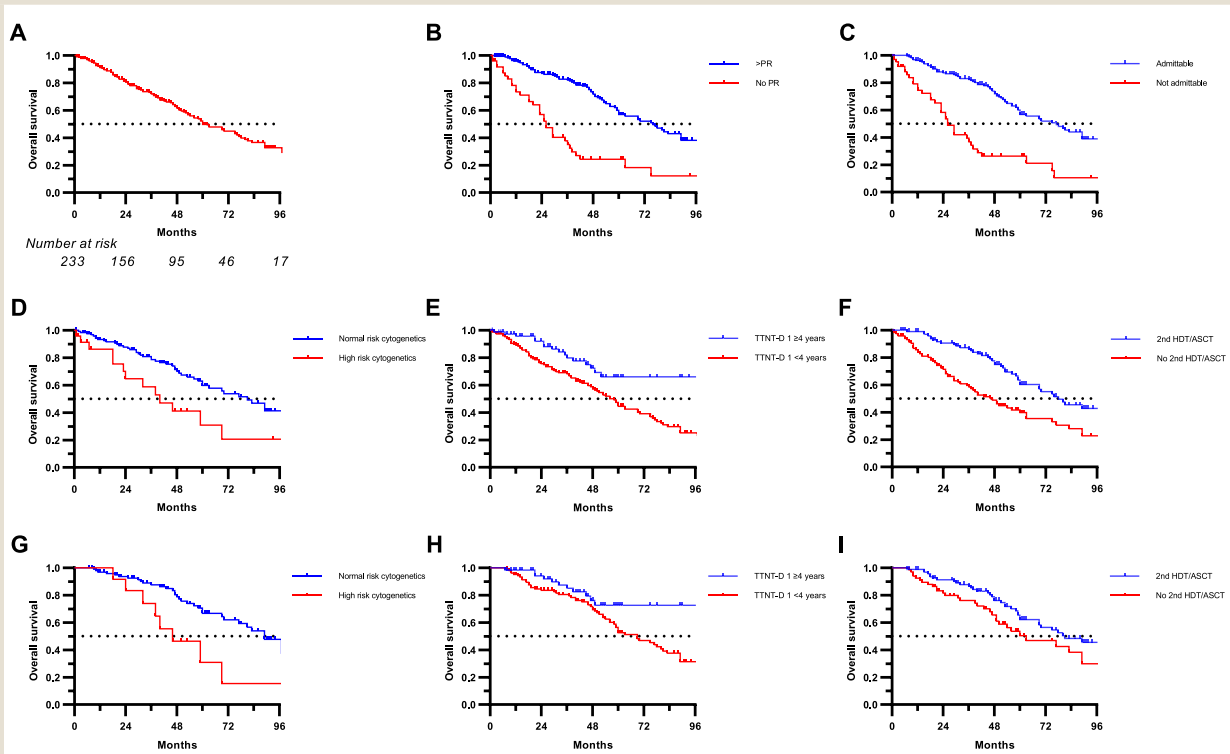
Supplemental Figure 4

Overall survival. (A) Total: The median OS is 60 months (95% CI, 49-71 months). (B) Response re-induction: The median OS for a PR or better is 76 months (95% CI, 61-91 months) and for no PR is 26 months (95% CI, 21-31 months)(HR = 2,36; $P < .001$). (C) Landmark exclusions: The median OS for inclusion in the landmark analysis is 77 months (95% CI, 61-93 months) and for exclusion in the landmark analysis is 26 months (95% CI, 21-31)(HR = 3,38; $P < .001$; only univariable analysis). (D) cytogenetic risk: The median OS for absent high-risk cytogenetics is 81 months (95% CI, 64-98 months) and for present high-risk cytogenetics is 40 months (95% CI, 22-58 months)(HR = 2,02; $P = .028$). (E) TTNT-D 1 groups: The median OS for a TTNT-D1 of ≥ 4 years is not reached (95% CI, not reached) and < 4 years is 56 months (95% CI, 48-64 months)(HR = 2,50; $P < .001$). (F) Second HDT/ASCT: The median OS for treatment with HDT/ASCT is 78 months (95% CI, 48-92 months) and for treatment without HDT/ASCT is 47 months (95% CI, 36-58 months)(HR = 1,72; $P = .018$). (G) Landmark analysis cytogenetic risk: The median OS for absent high-risk cytogenetics is 89 months (95% CI, 77-101 months) and for present high-risk cytogenetics is 46 months (95% CI, 23-69 months)(HR = 2,53; $P = .021$). (H) Landmark analysis TTNT-D 1 groups: The median OS for a TTNT-D1 of ≥ 4 years is not reached (95% CI, not reached) and < 4 years is 69 months (95% CI, 54-84 months)(HR = 1,90; $P = .041$). (I) Landmark analysis second HDT/ASCT: The median OS for treatment with HDT/ASCT is 80 months (95% CI, 58-102 months) and for treatment without HDT/ASCT is 63 months (95% CI, 38-88 months)(HR = 1,76; $P = .020$).

Abbreviations: HDT/ASCT: high dose therapy and autologous stem cell transplantation; PR: Partial response; TTNT-D 1: Time to next treatment or death 1.



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Supplemental Table 5 Post-Transplantation Complications

	First HDT/ASCT	Second HDT/ASCT
	n (%)	n (%)
Total	*111 (100)*	*111 (100)*
Complications		
Any	87 (83.7)	86 (81.9)
Mucositis	71 (71.7)	71 (70.3)
Needing TPN	53 (58.9)	54 (54.0)
Fever	74 (70.5)	80 (76.9)
Delirium/Confusion	0 (0.0)	7 (6.6)
Thrombosis	4 (3.7)	0 (0.0)
ICU-admission	1 (0.9)	4 (3.8)
Transplantation-related mortality	0 (0.0)	1 (0.9)
Infections		
None	47 (43.9)	36 (34.6)
Any	60 (56.1)	68 (65.4)
1 Infection	40 (37.4)	30 (28.8)
> 1 infection	20 (18.7)	38 (36.5)
Total amount of infections (average per patient)	84 (0.76)	124 (1.12)
Respiratory	19 (22.6)[a]	20 (16.1)[a]
Staphylococcal	20 (23.8)[a]	20 (16.1)[a]
HSV	17 (20.2)[a]	20 (16.1)[a]
Admission and regeneration (median time in days (range))		
Admission time	22 (14-59)	20 (14-45)
Time until Thrombocytes > 50×10^9/L	15 (9-648)	14 (9-167)
Time until Granulocytes > 0.5×10^9/L	16 (7-57)	15 (10-119)
Secondary primary malignancies		
Total	N.A.	6 (5.4%)[b]

When data is missing for a variable, the percentages are based on the number of available patients.
Abbreviations: HDT/ASCT: high dose therapy and autologous stem cell transplantation; HSV: Herpes simplex virus; ICU: Intensive care unit; n: number of patients; N.A.: Not applicable; TPN: Total parenteral nutrition.
[a]Percentage of total amount of infections.
[b]Excluding nonmelanoma skin cancer; consisting of n = 2 myelodysplastic syndrome, n=2 glioblastoma, n=1 esophageal carcinoma and n=1 prostate carcinoma.

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