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Myeloablative Radioligand Therapy Targeting C-X-C Motif Chemokine Receptor 4 in Advanced Multiple Myeloma

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Background: Markedly expressed on hematopoietic stem cells, C-X-C motif chemokine receptor 4 (CXCR4)-directed radioligand therapy (RLT) has been used in relapsed/refractory (r/r) MM to prepare for hematopoietic stem cell transplantation (HSCT). We aimed to determine the myeloablative efficacy of CXCR4 RLT in MM patients and assessed the safety profile of this treatment.

Methods: Thirty-eight patients with r/r MM were treated with 40 cycles of CXCR4-targeting [^{90}Y]Y-PentixaTher or [^{177}Lu]Lu-PentixaTher. Myeloablative dynamics were closely monitored by examining hematologic parameters before the application of RLT (day 1), on day 2, and on the start day of conditioning chemotherapy (CON, median day 10). Laboratory parameters evaluating organ toxicity were collected and categorized following the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Cairo-Bishop classification was also applied to identify patients experiencing laboratory tumor lysis syndrome (TLS) caused by RLT. After CON, we determined the rate of patients receiving hematopoietic stem cell transplantation (HSCT) followed by successful neutrophile engraftment.

Results: Forty cycles of CXCR4-directed RLT were applied. Myeloablative effects resulted in an 81.8% decline in leukocytes and a 69.4% decrease in neutrophil levels till the day of CON ($P < 0.0001$, respectively), followed by platelets (63.1%; $P < 0.0001$) and hemoglobin (9%; $P = 0.002$). We observed 58 AE Events (1/58 [1.7%], ≥ grade 3). CON could be applied successfully after 39/40 (97.5%) cycles. After CON, in 39/39 (100%) of the cycles, HSCT was conducted, and successful neutrophil engraftment was reached after 37/39 (94.9%) of these cycles.

Conclusions: CXCR4-directed RLT exerted relevant myeloablative effects. When performing HSCT after applying additional CON, successful neutrophile engraftment was reached in the vast majority of the cases.

Key Words: [^{90}Y]Y-PentixaTher, [^{177}Lu]Lu-PentixaTher, [^{68}Ga]Ga-PentixaFor, CXCR4, C-X-C motif chemokine receptor 4, radioligand therapy, multiple myeloma

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Despite encouraging advances in the treatment of multiple myeloma (MM) over the last 2 decades, management of the plasma cell neoplasm remains a challenging task.[1] Although allogeneic hematopoietic stem cell transplantation (HSCT) offers a potentially curative option in selected patients[2] and recently developed therapeutic agents continue to improve patient survival,[3] persisting high rates of morbidity and mortality underline the unmet need for new therapeutic strategies further improving patient safety and outcome.[4]

C-X-C motif chemokine receptor 4 (CXCR4) plays a pivotal role in the expansion of MM in the bone marrow (BM), while its ligand CXCL12 mediates invasion out of the BM in a gradient-dependent manner.[5,6] In this regard, a recent study reported that minimal residual disease is characterized by increased CXCR4 levels in their plasma cell clones.[7] Those properties render this chemokine receptor subtype as a suitable theranostic target in hematologic neoplasms[8] and thus, CXCR4-targeted PET followed by radioligand therapy (RLT) has already provided promising results in an end-stage disease setting,[9–11] including small cohorts of MM patients.[10,12]

In addition to an antimyeloma efficacy,[13] CXCR4-directed RLT exerts myeloablative effects as this chemokine receptor subtype is also overexpressed on hematopoietic stem cells.[14] As such, after RLT-orchestrated eradication of the stem cell niche, respective protocols included a conditioning regimen (CON, to "deepen" the desired aplasia) followed by HSCT and engraftment.[15] In this regard, a recent study has already investigated the extent of BM ablation in lymphoma patients and reported a significant decline of respective laboratory parameters along

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with successful HSCT in a substantial portion of treated subjects.[15] Patients could therefore potentially benefit from reducing or even replacing myeloablative chemotherapeutic CON through the application of RLT when preparing for HSCT.[13,15]

In MM, detailed information on myeloablative efficacy has not been provided yet, in particular on the RLT-mediated ablative impact independent from subsequent CON. Moreover, information on the safety profile of CXCR4 RLT in MM, including tumor lysis syndrome (TLS), is rather sparse.[10] Therefore, our study aimed to assess myeloablative efficacy and success rates of HSCT in a large cohort of relapsed/refractory (r/r) cases of MM who received CXCR4-directed RLT. We collected hematologic laboratory parameters throughout the therapy course until the day of subsequent CON. We also monitored laboratory markers of end-organ toxicity to report on RLT-caused adverse events (AE), along with occurrence of laboratory-based TLS.

PATIENTS AND METHODS

General

We retrospectively analyzed 38 patients with r/r MM, who had received 40 cycles of CXCR4-directed RLT (with [^{90}Y]Y- or [^{177}Lu]Lu-PentixaTher), followed by chemotherapeutic CON and autologous or allogeneic HSCT.

Parts of this cohort have already been examined in[9,10,12,13] without further assessing myeloablative efficacy and dynamics, success rates of HSCT, occurrence of TLS, and organ-based toxicity over time on a larger basis. CXCR4-directed RLT was offered on a compassionate-use basis after exhausting all standard therapy regimens. Application of RLT was then conducted according to the German Pharmaceutical Act (§13.2b) as a conditioning regimen, accompanied by subsequent chemotherapeutic CON preparing for allogeneic or autologous HSCT. Neutrophil engraftment was defined as neutrophil counts of $>0.5 \times 10^9$/L for 3 consecutive days after HSCT.[16,17] All patients were informed in detail about potential risks of the diagnostic and therapeutic procedures and signed written informed consent. The local ethics committee waived the need for approval for this analysis due to the retrospective character (# 20220103 01).

[^{68}Ga]Ga-PentixaFor PET/CT and Preparation for RLT

To identify suitable candidates for CXCR4-RLT, CXCR4-directed PET/CT was performed. The respective radiotracer [^{68}Ga]Ga-PentixaFor was synthesized in-house, as described before.[10] We applied a median of 128.5 (38–169) MBq and conducted PET/CT scans after 60 minutes using a Siemens Biograph mCT 64 or 128 system (Siemens Healthineers, Erlangen, Germany). In total, 38/40 (95%) scans were available for analysis, and before RLT, dosimetry was performed.[13]

To minimize undesirable side effects, a nephroprotective solution containing each 25 g/L arginine and lysine (2 L in total) was additionally administered in accordance with a practical guidance for receptor-targeted RLT.[18] The nephroprotective regimen was later further enforced by an additional TLS prophylaxis protocol, consisting of 300 mg allopurinol daily and 2 L of a balanced full electrolyte or isotonic solution over a period of 24 hours the day after administration of RLT. We also performed fluid balancing including weight measurement twice daily. Rasburicase (0.2 mg/kg bodyweight) was applied instead of allopurinol in high-risk patients and in the case of hyperuricemia following therapy.[19] During follow-up, patients were scheduled for application of chemotherapeutic CON and corresponding HSCT at our Department of Hemato-Oncology.

Examining Myeloablative Dynamics and Efficacy

To further investigate myeloablative dynamics and efficacy, we considered hematological laboratory parameters at 3 time points, if available. Laboratory values on the day of RLT before administration of [^{177}Lu]Lu- or [^{90}Y]Lu-PentixaTher were chosen as the starting point (day 0). Day 2 (earliest possible time point of discharge from the radioisotope ward) and the start day of CON were selected as further time points in concordance with the treatment algorithm. If no CON was performed, the median day of the remaining patients (ie, day 10) was selected as the reference time point.[15] As a part of our clinical routine, blood samples to determine hemoglobin (g/dL), platelet, leukocyte, and neutrophil levels (in 1000/μL, each) were taken using dipotassium-ethylenediaminetetraacetic acid (EDTA) tubes (Sarstedt, Nuembrecht, Germany). A fully automated modular analyzer (Sysmex XN-9000, Kobe, Japan) was used to further process collected blood samples, as described in.[20]

Monitoring of Laboratory Adverse Events and TLS

At the time points day 0, day 2, and day of CON, as described above, we collected renal functional parameters [creatinine (in mg/dL), estimated glomerular filtration rates (GFR); in mL/min/1.73 m^2; using the "Modification of Diet in Renal Disease" (MDRD) study equation][21] and functional liver parameters (glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, and gamma-glutamyl transferase; in U/L, each). To classify potential AE, we applied the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).[22] To detect cases of TLS, blood samples were analyzed regarding levels of uric acid (in mg/dL), calcium, phosphate, and potassium (in mmol/L, each). We then applied the laboratory Cairo-Bishop-Definition, with TLS criteria being fulfilled with at least 2 of the following changes: 25% increase in either uric acid, potassium and phosphate or a 25% decrease in calcium.[23] All blood parameters were collected using serum-gel tubes (Sarstedt, Nuembrecht, Germany), and the respective analysis was performed using a Roche cobas analyzer (Basel, Switzerland).[20]

Statistical Analysis

GraphPad Prism version 10.4.0 (GraphPad Software, Boston, MA) was used to conduct statistical analyses. Median and range (minimum – maximum) are displayed for descriptive results. For the statistical analysis of myeloablative efficacy and dynamics, we considered both percentual and absolute changes in laboratory parameters. The ROUT-Method was applied to check for outliers in laboratory parameters, excluding the analyzes for adverse events after CTCAE v5.0 and the evaluation of TLS following the Cairo-Bishop-classification. The Wilcoxon matched-pairs signed rank test was performed to compare between baseline and follow-up values. Statistical significance was considered for P values <0.05.

RESULTS

Patient Characteristics

In total, 34/40 (85%) cycles were conducted using [^{90}Y]Y-PentixaTher (median activity of 5.2 [2.2–7.3] GBq). The remaining 6/40 (15%) cycles were carried out applying a median of 12.25 (7.6–23.5) GBq of [^{177}Lu]Lu-PentixaTher. Detailed patient characteristics are depicted in Table 1.

Myeloablative Efficacy

After the application of CXCR4-directed RLT, a 10% decrease in leukocyte levels compared to day 0 could be observed at day 2 ($P = 0.008$). On the day of CON, a drop in leukocyte counts by 81.8% ($P < 0.0001$) to baseline was obtained. Comparable results could be noted for neutrophil levels, with a significant drop till CON (69.4%, $P < 0.0001$). Neutrophil levels lower than 0.5 $\times 10^9$/L were reached after 19/40 (47.5%) cycles even before the application of additional chemotherapeutic CON. Significant decreases till the day of CON were also recorded for platelet (63.1%, $P < 0.0001$) and hemoglobin levels (9%, $P = 0.002$). Figure 1 and Table 2 provide a detailed overview.

Organ Toxicity

During or shortly after the application of RLT, no immediate adverse reactions were recorded. GFR and creatinine showed a beneficial tendency when comparing median baseline values and median levels at CON (creatinine: −9.7%, GFR: +12.1%; $P < 0.0001$, respectively), indicative of the effectiveness of the applied nephroprotective and TLS protocols. Liver enzymes revealed comparable results, as all investigated laboratory parameters showed a decrease till CON (gamma-glutamyl transferase: −16.1%, $P = 0.0097$; glutamic oxaloacetic transaminase: −10.4%, $P = 0.051$; glutamic-pyruvic transaminase: −29.7%, $P = 0.0001$; Fig. 2 and Table 2).

Classifying changes in laboratory parameters after CTCAE v5.0, 58 nonhematologic AE were observed, with no grade 3 and 4 AE. In 1/58 (1.7%), a grade 5 acute kidney injury was observed, caused by a fulminant TLS before the application of CON. The vast majority of recorded AE, however, were grade 1 and 2 [57/58 (98.3%), Table 3].

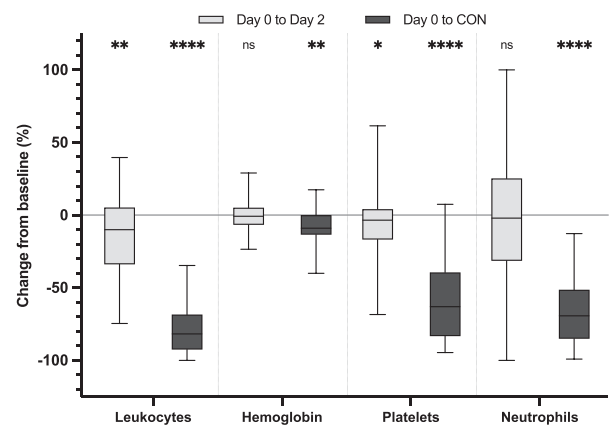

FIGURE 1. Myeloablative dynamics after the application of CXCR4-directed RLT. Boxplots display median % changes from day 0 (day of RLT) to day 2 as well as to the day of CON, whiskers indicating the respective range. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

TABLE 1. Patient Characteristics

Age (y)	
Median	59.5
Range	32–76
Sex, N/n (%)	
Male	22/38 (57.9)
Female	16/38 (42.1)
Myeloma subtype, N/n (%)	
IgG Kappa	8/38 (21.1)
IgG Lambda	8/38 (21.1)
Kappa light-chain	8/38 (21.1)
IgA Lambda	6/38 (15.8)
IgA Kappa	5/38 (13.2)
IgM Kappa	1/38 (2.6)
Lambda light-chain	1/38 (2.6)
Nonsecretory	1/38 (2.6)
Disease duration (y)	
Median	4.46
Range	0.86–16.52
Previous treatment lines (n)	
Median	6
Range	2–10
Prior HSCT, N/n (%)	
Any	37/40 (92.5)
Autologous	*37/37 (100)*
Allogeneic	*0/40 (0)*
HSCT (n)	39/40 (97.5)
Autologous	37/39 (94.9)
Allogeneic	2/39 (5.1)

Data on prior HSCT and HSCT is reported as a percentage of all cycles of conducted RLT.

HSCT indicates hematopoietic stem cell transplantation; n, number; y, year.

TABLE 2. Dynamics of Laboratory Parameters Relevant for Myeloablative Effects, Off-target Effects and Tumor Lysis Syndrome

	Day 0 to day 2		Day 0 to CON	
Parameter	**%-Change**	***P***	**%-Change**	***P***
Myeloablative effects				
Leukocytes	−10	**0.008**	−81.8	**< 0.0001**
Hemoglobin	−0.8	0.908	−9	**0.002**
Platelets	−3.4	**0.046**	−63.1	**< 0.0001**
Neutrophils	−2.1	0.651	−69.4	**< 0.0001**
Off-target eEffects				
Creatinine	0.3	0.665	−9.7	**< 0.0001**
GFR	0	0.729	12.1	**< 0.0001**
GGT	−8.2	**0.015**	−16.1	0.0097
GOT	−2.3	0.961	−10.4	0.051
GPT	−9.9	**0.048**	−29.7	0.0001
Tumor lysis syndrome				
Uric acid	−25.8	**< 0.0001**	−30.1	**< 0.0001**
Potassium	−5.6	0.099	−2.6	0.024
Phosphate	1.9	0.638	−13.7	0.003
Calcium	0	0.717	0	0.524

Median percentage changes of laboratory parameters occurred between baseline (Administration of RLT, day 0), day 2 after RLT, and day of additional chemotherapeutic conditioning (CON).

Significant *P*-values are marked in bold.

GFR indicates glomerular filtration rate; GGT, γ-glutamyltransferase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase.

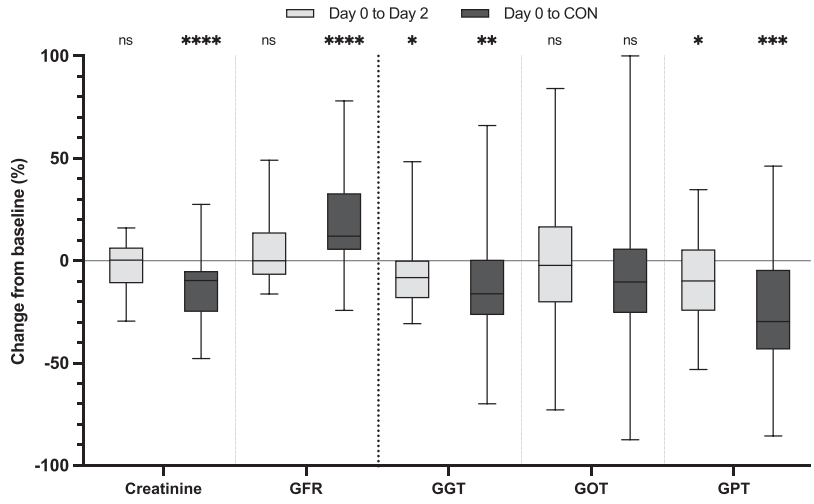

FIGURE 2. Laboratory-based short-term organ toxicity after CXCR4-directed RLT. Boxplots display median % changes from day 0 (day of RLT) to day 2 as well as to the day of CON, whiskers indicating the respective range. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. GFR indicates glomerular filtration rate; GOT, glutamic-oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase; GGT, γ-glutamyltransferase.

Tumor Lysis Syndrome

Based on laboratory values following the Cairo-Bishop definition, none of the investigated patients fulfilled the criteria of a TLS. However, as mentioned above, one patient developed a clinical TLS resulting in a lethal case of renal failure and malignant pleural effusion. Overall, analyzing parameters in all conducted cycles of RLT, no significant unfavorable changes in laboratory values could be observed, while for uric acid even a significant decrease (−30.1%; < 0.0001) relative to baseline could be recorded (Fig. 3; Table 2).

CON, HSCT, and Neutrophil Engraftment

Following RLT, additional chemotherapeutic CON was successfully administered after a median of 10 (4–30) days in 39/40 (97.5%) cycles. Median 14(12–32) days after CXCR4-directed RLT, HSCT could then be performed after 39/39 (100%) of remaining therapy cycles. In 37/39 (94.9%) cases, an autologous HSCT was conducted. Allogeneic HSCT was performed in 2/39 (5.1%) cases. Neutrophil engraftment was reached in 37/39 (94.9%) cases. Two heavily pretreated patients (5 and 7 prior therapy regimens including 1 and 4 previously performed HSCT; median disease duration 4.34 y) died due to infectious complications during neutropenia before successful engraftment could be reached.

TABLE 3. Laboratory-defined Adverse Events (AE) Occurring Between Day of RLT Until the Start of Additional Chemotherapeutic Conditioning (Based on CTCAE v5.0)

	Grade 1/2	Grade 3/4	Grade 5
All events	57	0	1
Hypophosphatemia	16	0	0
Hypocalcemia	7	0	0
Hypokalemia	5	0	0
Hyperphosphatemia	2	0	0
Hyperkalemia	2	0	0
Hypercalcemia	0	0	0
Creatinine	5	0	0
GFR	3	0	0
Acute kidney injury	0	0	1
GOT	6	0	0
GPT	2	0	0
GGT	6	0	0
Hyperuricemia	3	0	0

No AE grade 3/4 was observed, and only 1 grade 5 AE was caused by tumor lysis syndrome, resulting in a lethal case of renal failure.

GFR indicates glomerular filtration rate; GGT, γ-glutamyltransferase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase.

DISCUSSION

Assessing myeloablative efficacy, CXCR4-directed RLT resulted in a drop of more than 81% in leukocyte levels until the day of CON, with comparable dynamics observed for neutrophil levels. For thrombocyte and hemoglobin levels;

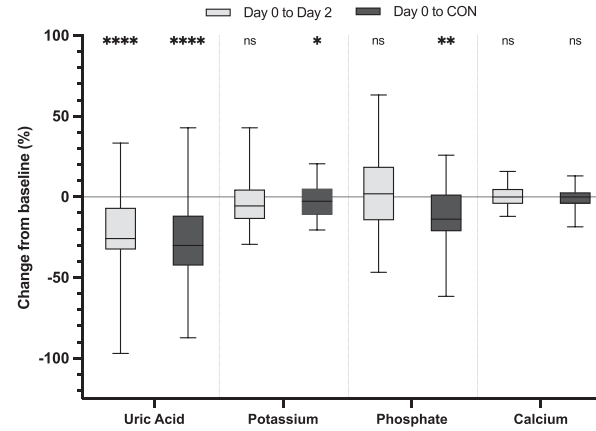

FIGURE 3. Laboratory TLS parameters after CXCR4-directed RLT. Boxplots display median % changes from day 0 (day of RLT) to day 2 as well as to the day of CON, whiskers indicating the respective range. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

however, a respective decline was less pronounced. In all patients having received CON after RLT, autologous or allogeneic HSCT could be conducted with successful neutrophil engraftment after > 94% of the cycles.

Our analysis revealed promising results regarding the myeloablative efficacy of CXCR4-directed RLT, with leukocyte and neutrophil levels dropping up to 81.8% and 69.4% till the day of CON. In over 47% of cases, neutrophil levels even fell below 0.5×10^9/L till the day of CON, hinting at a substantial myeloablative effect exclusively attributable to CXCR4-directed RLT. Thus, one might envision the application of RLT as a sole CON regimen prior to HSCT, eventually replacing chemotherapeutic regimens or at least allowing for its dose reduction in a variety of clinical scenarios requiring HSCT. Such chemotherapy-free conditioning regimes in preparation for HSCT are already the subject of intensive research, as more specific therapeutics could potentially prevent organ and genotoxic side effects of chemotherapy.[24,25] Among others, monoclonal antibodies targeting surface antigens expressed on white blood cells or hematopoietic stem cells, eg, CD45 or KIT, are being investigated as an alternative for chemotherapeutic CON.[24,26,27] For CD45, even the administration of an antibody-radionuclide conjugate has been examined in leukemia and lymphomas followed by HSCT, with or without concomitant chemotherapy, achieving promising results.[28–30] In a comparable manner, CXCR4-directed radioligands could therefore potentially achieve a specific eradication of CXCR4-positive white blood cells/hematopoietic stem cells, preparing for autologous or allogeneic HSCT, with the favorable side effect profile demonstrated in the present and other studies.[13,15] Further clinical experience regarding the feasibility of achieving myeloablation and successful engraftment after HSCT using ionizing radiation has already been gained in the context of total body irradiation (TBI).[25] However, this procedure is characterized by an unfavorable side effect profile due to the unspecific whole-body radiation, possibly promoting side effects in every organ system.[31] Therefore, the specific application of radiation by endogenous targeted RLT could possibly prevent unwanted effects in comparison to TBI.

When investigating alternative strategies to prepare for HSCT, sufficient myeloablation without extensively damaging the supporting niche of the BM is desirable, thereby providing an essential prerequisite for the successful engraftment of transplanted stem cells.[32] In our study, in up to 94% cycles with successful administration of additional chemotherapeutic CON after RLT, sustainable neutrophil engraftment was observed, indicating that even combined strategies (CXCR4-RLT + CON) do not damage the supporting BM niche to an extent, where engraftment of transplanted stem cells would be totally hampered. Our results are therefore in line with preclinical examinations regarding this aspect.[32] Moreover, the high rate of successful HSCT after CXCR4-directed RLT in our cohort also suggests excellent suitability for patients having received prior HSCT. Of note, before 92.5% of cycles in our study, patients had already undergone up to 4 courses of HSCT as part of previous treatment, indicating that high success rates can be achieved using CXCR4-directed RLT as a conditioning regimen even in heavily pretreated patients.

To enable individualized approaches, the prognostic value of pretherapeutic PET or dosimetry regarding myeloablative efficacy should be further investigated. This may then provide a substantial pretest probability for identifying patients suitable for a solely radioligand-based CON before HSCT or combination strategies, preferably in a prospective trial setting.

In addition to its myeloablative efficacy, we obtained favorable results regarding short-term organ toxicity after the application of CXCR4-directed RLT, with renal and hepatic functional parameters showing no sign of relevant liver or kidney toxicity when assessing absolute and percentual changes. Applying CTCAE v5.0, 57/58 (98.3%) of AE recorded were less than or equal to grade 2, indicating a favorable side effect profile. However, in the present heavily pretreated cohort, lethal complications during the course of therapy occurred in 3/40 (7.5%). One subject experienced a Grade 5 acute kidney injury due to the event of a clinical TLS before CON. In this regard, TLS prophylaxis protocol may be an important step toward risk reduction,[23] including close monitoring during therapy course. Moreover, in 2 cases, lethal infections during neutropenia before successful engraftment occurred. When performing HSCT, infections remain one of the main causes of treatment-related mortality,[33] even though the risk for lethal infectious complications has been successfully reduced over the last decades.[34] In a large retrospective observational study based on the European Society for Blood and Marrow Transplantation (EBMT) database, Styczyński et al[33] report on a cumulative incidence of lethal infectious complications during the first 30 days after HSCT of 1.09 for autologous and 2.25 for allogeneic transplants performed in leukemia patients between 2002 and 2015. In MM, when applying chemotherapeutic CON (± TBI) to prepare for allogeneic HSCT, Crawley et al[35] report on treatment-related mortality by infectious complications in 39/229 (17%) patients in the first 100 days after HSCT. When comparing the risk of life-threatening infections to other studies using radionuclide compounds in preparation for HSCT in MM, Tuazon et al[30] report on grade 4 sepsis in 7% of patients when applying a CON regimen consisting of the CD45 antibody-radionuclide compound [^{90}Y]Y-DOTA-BC8, fludarabine, and low-dose TBI preparing for allogeneic HSCT in relapsed MM patients. Although our study reports on extensively pretreated MM patients in an end-stage disease setting, the overall mortality rate of 7.5% in our study highlights the importance of a close collaboration between nuclear medicine physicians and hemato-oncologists in patient care during the different phases of the treatment algorithm to minimize patients' risk of morbidity and mortality. In addition, patients' suitability for a myeloablative regimen should be carefully assessed beforehand, considering the possibly prolonged neutropenic phase when performing both myeloablative RLT and chemotherapeutic CON before HSCT. In this regard, the shorter half-life of Yttrium-90 relative to Lutetium-177 may further reduce the risk of lethal outcomes due to shorter neutropenic phases, as the time frame between CXCR4-targeted RLT and CON can be reduced.[8]

Our study has several limitations, including its retrospective design. In addition, laboratory parameters reflecting myeloablation and organ toxicity could only be assessed at 3 time points during the therapy course. Furthermore, due to the application of an additional chemotherapeutic CON, the myeloablative activity of CXCR4-directed RLT could only be assessed at this certain time point. Nevertheless, we hereby report on a large cohort of MM patients treated with CXCR4-directed RLT to date, potentially providing valuable insights on myeloablative efficacy and dynamics, short-term organ toxicity, and success rates of HSCT in heavily pretreated patients.

CONCLUSIONS

Chemokine receptor-targeted RLT led to a relevant decrease of leukocyte and neutrophil levels, indicative of effective bone marrow ablation when combined with CON. Of note, in almost half of the cycles, neutrophils fell below 0.5 $\times 10^9$/L till the day of CON, and thus, future research should intensively investigate the possibility of a solely RLT-based conditioning preparing for HSCT. Successful neutrophil engraftment was observed after >94% of performed HSCT cycles.

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