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Outcome of patients with mantle cell lymphoma after autologous stem cell transplantation in the pre-CAR T-cell era

Letter

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Abstract

Introduction: Mantle cell lymphoma (MCL) patients can be treated with intensive induction therapy, followed by high dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) for consolidation and subsequent anti-CD20 maintenance. For patients relapsing after bruton tyrosine kinase (BTK) inhibitors, CAR T-cell therapy became available in late 2020 fueling the interest in outcomes of relapsing MCL patients.

Methods: We retrospectively analyzed the outcome of MCL patients receiving HDCT/ASCT at our center between 2000 and 2021, thus, before availability of CAR-T cells.

Results: We identified 97 MCL patients undergoing HDCT/ASCT in this period with a median follow-up of 52 months. 43 (44%) patients ultimately relapsed, and 29 (30%) have died. The median progression-free survival (PFS) for the entire cohort was 48 months and overall survival (OS) was 202 months. Relapsing patients had a median PFS of only 28 months and median OS of 105 months. The OS of relapsing patients receiving BTK inhibitors was 148 versus 78 months in patients who never received BTK inhibitors (p=0.1175).

Conclusion: Even after HDCT/ASCT, a substantial proportion of MCL patients will relapse and ultimately die of the disease, emphasizing the need for new therapeutic options including CAR T-cell treatment for this lymphoma subtype.

Key words: Mantle cell lymphoma (MCL), lymphoma, autologous stem cell transplantation (ASCT), CAR T-cell, outcome.

Letter

Patients with mantle cell lymphoma (MCL) are commonly treated with induction immunochemotherapy, e.g. alternating cycles of R-CHOP and R-DHAP, followed by autologous stem cell transplantation (ASCT) and anti-CD20 maintenance [1-3]. High-dose chemotherapy before ASCT is BEAM (carmustine, etoposide, cytarabine and melphalan), whereas recent reports replaced carmustine with bendamustine (BeEAM) with at least similar efficacy, but a different toxicity profile [4].

In relapsed or refractory (r/r) MCL, mTOR- and bruton-tyrosine-kinase (BTK) inhibitors are used. PFS with the BTK inhibitor ibrutinib is longer as compared to the mTOR-inhibitor temsirolimus, particularly after one prior treatment line [5,6]. However, PFS rates in r/r MCL patients decrease with each treatment line [7]. In contrast, CAR T-cell therapy with Tisagenlecleucel or Axicabtagene ciloleucel has shown durable remission rates in relapsed DLBCL patients with overall response (ORR) of 52-82% and CR rates of 40-59% [8-10]. For r/r MCL patients, the FDA approved brexucabtagene autoleucel (Tecartus®) in late 2020 [11,12], and the EMA granted this new therapy a conditional marketing authorization [13].

We retrospectively investigated the outcome of MCL patients undergoing HDCT/ASCT in a real-world scenario in the pre-CAR T-cell era to better define the potential benefit which r/r MCL patients may derive from this new option. In this single-center study, we analyzed all consecutive adult MCL patients undergoing HDCT/ASCT at Bern University Hospital between 01/2000 and 04/2021, thus, before brexucabtagene autoleucel became available in Switzerland.

Patients were separated into two groups: The first group had relapsing or progressive MCL before or after ASCT (“relapsed” patients). The second group was in complete or

partial remission until last follow-up, never had overt progression, or died of reasons unrelated to lymphoma or its treatment ("non-relapsed" patients). The endpoints were progression-free (PFS) and overall survival (OS). The study was approved by a decision of the ethics committee Bern, Switzerland (decision number KEK #321/2014; with decision date March 20, 2015).

We identified 97 consecutive MCL patients (95 of those had received rituximab during the induction treatment) receiving HDCT/ASCT (patient characteristics in **Supplemental Table S1**). 43 patients (44%) had relapsing or progressive disease ("relapsed" patients), while 54 patients (56%) remained in ongoing first remission or had achieved at least partial remission ("non-relapsed" patients) (**Supplemental Table S1**).

HDCT was BEAM in 57 (59%) patients, while 40 (41%) received BeEAM. Patients undergoing HDCT at relapse mostly received BEAM (84% of all cases), while BeEAM was only used in 16%. In contrast, non-relapsed patients received BEAM in 39% and BeEAM in 61% (**Table 1A**). Most relapsed patients had HDCT/ASCT before 2013, when only BEAM was used. After HDCT/ASCT, most patients received rituximab maintenance (n=93/97; 96%), whereas other maintenance therapies were not used.

The median follow-up was 52 months (range, 6 to 260 months). Relapsed patients had a longer median follow-up (86 months) following diagnosis than non-relapsed patients (33 months), as most non-relapsed patients were diagnosed later with shorter follow-up.

Remission status was determined at day 100 post-transplant. 78 patients (80%) achieved CR, 11 patients (11%) achieved PR (n=7; 7%) or SD (n=4; 4%). The remaining 8 patients died before day 100 (n=2; 2%) or died earlier (n=6; 6%). Until

April 2021, 29 patients (30%) have died: 25 of progression (n=24; 25%) or due to lymphoma treatment (n=1; 1%); four patients (4%) died due to unrelated reasons **(Table 1B)**. Median PFS from diagnosis was 48 months **(Figure 1A)** for all patients, and OS was 202 months **(Figure 1B)**.

Median PFS from initial diagnosis in relapsed patients was 28 months versus not reached in non-relapsed patients, and PFS rate at 48 months (4 years from ASCT) was 16% versus 88% (p <0.0001, **Figure 1C**). Median OS in relapsed patients was 105 months versus not reached in non-relapsed patients, OS rate at 96 months (8 years from ASCT) was 52% versus 88% (p=0.0018; **Figure 1D**).

Relapsing patients had a median PFS of only 18 months after the first relapse (PFS2) versus 48 months from diagnosis to first relapse (PFS1, **Supplemental Figure S1A**). Median OS of all patients was 202 months (OS1). After first relapse, the median OS was only 64 months from the time of first relapse (OS2, **Supplemental Figure S1B**). Patients with ≥2 prior lines (n=20; 21%) tended to have worse OS than those with one prior treatment (n=77; 79%; not significant). OS after 96 months (8 years after ASCT) was 69% in patients with one line, and 60% in patients with ≥two prior lines (p=0.3918; **Supplemental Figure S1C**).

Importantly, 16 of 43 relapsing patients (37% of this subgroup) received ibrutinib. Median OS of relapsed patients with ibrutinib was 148 months versus 78 months in patients never receiving ibrutinib, with OS at 96 months (8 years after ASCT) of 65% versus 44 (p=0.1175; **Supplemental Figure S1D**).

Brexucabtagene autoleucel is currently going to become available in Europe for r/r MCL patients. This study investigated the outcome of 97 MCL patients undergoing

HDCT/ASCT in the pre-CAR T-cell era to better characterize the patients that may benefit from this new option.

First, 70% of all MCL patients in our study were alive at the last follow-up, whereas 30% had died, predominantly due to the underlying lymphoma. Whereas the outcome of non-relapsed patients was favorable with median OS and PFS not being reached after a reasonably long follow-up, relapsing patients showed median PFS of only 28 months and OS of 105 months. In particular, patients with ≥2 lines before HDCT/ASCT had adverse outcomes, confirming previous reports [6,7]. Our results emphasize the potential of HDCT/ASCT for MCL patients, but demonstrate as well the limitation of this consolidation approach particularly for relapsing disease.

Relapsed patients received BeEAM in 16% of cases, but in 61% of all first-line HDCT patients, whereas all other patients received BEAM reflecting a shift towards first-line consolidation with BeEAM in the recent part of the study. This may cause a bias due to different follow-up in the patients before and after the introduction of BeEAM. The patients in the “BEAM only” period before 2013 may have developed more relapses due to the longer observation time. Hueso et al. compared 60 patients who received BeEAM to 108 patients who received BEAM. Especially in the low-risk MIPI group, the PFS was significantly better with BeEAM with a 3-year PFS rate of 84% versus 63% with BEAM. Although rituximab maintenance was more frequent in the BeEAM group, there may be a benefit for MCL patients receiving BeEAM [14]. Finally, rituximab maintenance was shown to prolong PFS and OS in MCL patients after HDCT/ASCT [15,16].

In our cohort, 37% of all relapsed patients effectively received ibrutinib. Our data in these patients are in accordance to previous reports. Rule et al. reported a longer PFS

in MCL patients who received ibrutinib as compared to temsirolimus (mTOR-Inhibitor) [6]. However, patients relapsing after BTK inhibitors showed poor OS of only 6-10 months [17].

Brexucabtagene autoleucel (Tecartus®) has shown promising results in patients with r/r MCL after several treatment lines including BTK inhibitors. r/r MCL patients had a PFS rate of 61% and OS rate of 83% after 12 months from CAR T-cell treatment [11]. Preliminary results of the TRANSCEND-NHL-001 study reported an encouraging ORR of 84% with lisocabtagene maraleucel (Liso-cel) for r/r MCL patients, associated to a lower incidence of CRS and neurotoxicity [18].

Nevertheless, our retrospective single-center study had several limitations, including a limited cohort size, and a follow-up over a long study period with inevitable time bias. Patients were referred from different Swiss sites, and the MIPI was introduced only in 2008. On the other hand, our study reports real-world patients in a consecutive design, and clearly identified the limitations of the currently available consolidation and maintenance approaches for MCL patients. Currently, CAR T-cell therapy for r/r MCL patients became available in some hospitals in an early access program at the beginning of 2021. Our study emphasizes the need to rapidly facilitate the access of this patient population to CAR-T cell treatment.

Conflict of interest: All authors declare no conflict of interest.

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Table 1A. Characteristics of CD34+ mobilization therapy and high dose chemotherapy (HDCT)/autologous stem cell transplantation (ASCT) in patients with or without relapse.

Parameter	All patients	Relapsed patients	Non-relapsed patients
Patients, n (%)	97 (100%)	43 (44%)	54 (56%)
Interval diagnosis to ASCT, months, median (range)	6 (4-79)	6 (4-79)	5 (4-52)
CD34+ mobilization therapy, n (%)			
DHAP	29 (30%)	9 (21%)	20 (37%)
Vinorelbine	28 (29%)	14 (33%)	14 (26%)
DHAO	14 (14%)	1 (2%)	13 (24%)
ESAP	9 (9%)	7 (16%)	2 (4%)
ICE	3 (3%)	3 (7%)	0 (0%)
Others*	14 (14%)	9 (21%)	5 (9%)
HDCT, n (%)			
BEAM	57 (59%)	36 (84%)	21 (39%)
BeEAM**	40 (41%)	7 (16%)	33 (61%)
Stem cell source, n (%)			
Peripheral blood	96 (99%)	42 (98%)	54 (100%)
Bone marrow	1 (1%)	1 (2%)	0 (0%)

* Other therapies: unknown (n=5), CHOP (n=3), gemcitabine (n=3), cyclophosphamide (n=2), cytarabine (n=1). ** BeEAM was first used in 2013.
DHAP: dexamethasone, high dose cytarabine, cisplatin. DHAO: dexamethasone, high dose cytarabine, Oxaliplatin. ESAP: etoposide, methylprednisolone, cytarabine, cisplatin. ICE: ifosfamide, carboplatin, etoposide HDCT: high dose chemotherapy. BEAM: carmustine, etoposide, cytarabine, melphalan. BeEAM: bendamustine, etoposide, cytarabine, melphalan

Table 1B. Clinical outcomes of MCL patients with or without relapse.

Parameter	All patients	Relapsed patients	Non-relapsed patients
Number of patients, n (%)	**97 (100%)**	**43 (44%)**	**54 (56%)**
Median follow up, months (range)	**52 (6-260)**	**83 (6-260)**	**33 (6-202)**
State of remission day 100*, n (%)			
Complete remission (CR)	78 (80%)	34 (79%)	44 (81%)
Partial remission (PR)	7 (7%)	5 (12%)	2 (4%)
Stable disease (SD)	4 (4%)	3 (7%)	1 (2%)
Progressive disease (PD)	0 (0%)	0 (0%)	0 (0%)
State of remission at last follow up, n (%)			
CR	55 (63%)	14 (33%)	41 (93%)
PR	4 (5%)	4 (9%)	0 (0%)
SD	0 (0%)	0 (0%)	0 (0%)
PD	0 (0%)	0 (0%)	0 (0%)
Mortalities (total), n (%)	**29 (30%)**	**25 (58%)**	**4 (7%)**
Progression, n (%)	24 (25%)	24 (56%)	0 (0%)
Therapy-related, n (%)	1 (1%)	1 (2%)	0 (0%)
Other**, n (%)	4 (4%)	0 (0%)	4 (7%)
Interval from ASCT, median, months (range)	34 (1-172)	36 (1-172)	19 (2-39)

* State of remission day 100 not yet available in 6 patients, 2 patients died before day 100. ** Other causes: pancreatic carcinoma (n=1), pulmonary infection (n=1), other infection (n=1), myocardial infarction (n=1).

Figure Legends

Figure 1. A: Progression-free and **B:** overall survival of the total cohort. **C:** Progression-free and **D:** overall survival in patients with relapse (continuous line) or without (dashed line).

Figure 1. A: Progression-free and **B:** overall survival of the total cohort. **C:** Progression-free and **D:** overall survival in patients with relapse (continuous line) or without relapse (dashed line).