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**Bendamustine-Etoposide-Cytarabine-Melphalan  
(BeEAM) versus  
Carmustine-Etoposide-Cytarabine-Melphalan (BEAM)  
chez les patients atteints de lymphome à cellules du  
manteau traités par autogreffe en première ligne : étude  
comparative rétrospective multicentrique des centres du  
Lymphoma Study Association (LYSA)**

Thomas Hueso

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**DU GRADE DE DOCTEUR EN MÉDECINE**

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Bendamustine-Etoposide-Cytarabine-Melphalan (BeEAM) versus. Carmustine-Etoposide-Cytarabine-Melphalan (BEAM) chez les patients atteints de lymphome à cellules du manteau traités par autogreffe en première ligne : Étude comparative rétrospective multicentrique des centres du Lymphoma Study Association (LYSA)

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## **Abréviations**

ARF : Acute renal failure

ASCT : Autologous stem cell transplantation

BCNU : Carmustine

BEAM : Carmustine, etoposide, cytarabine, melphalan

BeEAM : Bendamustine, etoposide, cytarabine, melphalan

CR : Complete remission

CIR : Cumulative incidence of relapse

MCL : Mantle cell lymphoma

MIPI : Mantle cell lymphoma international prognostic index

NHL : non-Hodgkin lymphoma

NRM : non-Relapse mortality

OS : Overall survival

PFS : Progression-free survival

PR : Partial response

SD/PD : Stable/progressive disease

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## Introduction

Le lymphome à cellules du manteau (LCM) représente 5 à 10 % des lymphomes B non Hodgkinien (LNH). Il est considéré à ce jour comme incurable et se caractérise par des rechutes itératives responsables d'un pronostic souvent sévère. Selon les caractéristiques clinico-biologiques de la maladie, la présentation ainsi que l'évolution peut être indolente ou agressive avec une survie globale à 5 ans variant de 85% à 17%.

Etant donné le risque élevé de rechute un traitement intensif est recommandé afin d'obtenir une réponse clinique profonde et durable. Ainsi, les patients jeunes sans comorbidités bénéficieront d'un traitement d'induction, suivi d'une intensification avec un conditionnement de greffe, puis une autogreffe de cellules souches hématopoïétiques (CSH).

Le traitement d'induction est essentiellement basé sur l'utilisation d'un anticorps anti-CD20 (rituximab) associé à une polychimiothérapie. Bien que plusieurs schémas d'induction soient proposés, l'association du rituximab et de la cytarabine couplé à d'autres chimiothérapies est à ce jour le traitement de référence afin d'atteindre la réponse complète avant l'autogreffe de CSH.

Le choix du conditionnement d'autogreffe reste sujet à controverse. L'irradiation corporelle totale peut être une option chez les patients n'ayant pas atteint la réponse complète après le traitement d'induction, avec néanmoins des toxicités secondaires importantes. Une polychimiothérapie associant de fortes doses carmustine (BCNU) d'étoposide, de cytarabine, et de melphalan (BEAM) reste le premier choix dans la majorité des centres. Depuis quelques années du fait des difficultés

d'approvisionnement et du coût croissant de la carmustine, des alternatives ont été proposées.

La bendamustine est un agent cytotoxique qui combine les propriétés des agents alkylants et des analogues des purines. Elle a montré son efficacité dans le traitement d'induction du LCM notamment chez les patients plus âgés ne pouvant bénéficier d'une autogreffe de CSH. La faisabilité de la bendamustine à la dose de 200 mg/m<sup>2</sup> en remplacement du BCNU (BeEAM) a été rapportée en 2011 sans toxicités notables chez des patients atteints de LNH en rechute. Cependant nous avons rapporté récemment la toxicité rénale de ce type de conditionnement chez 478 patients atteints de LNH. A ce jour, l'étude d'efficacité n'a pas pu être effectuée du fait de l'hétérogénéité des patients, de sous type histologique différents et du court suivi post-autogreffe.

Etant donné l'efficacité de la bendamustine dans le traitement d'induction des LCM et de la faisabilité du BeEAM, nous souhaitons par ce travail élargir notre connaissance sur l'efficacité de ce conditionnement dans une cohorte de patients atteints d'un LCM comparée à une cohorte de patients homogène traitée par BEAM.

**Article**

**Soumis à la revue *American Journal of Hematology***

## Title page

# **Bendamustine-EAM versus BEAM regimen in patients with mantle cell lymphoma undergoing autologous stem cell transplantation in the frontline setting: a multicenter retrospective study from Lymphoma Study Association (LYSA) centers.**

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## Abstract

The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) as conditioning regimen prior to autologous stem-cell transplantation (ASCT) remains the standard of care for patients with mantle cell lymphoma (MCL) who are eligible for transplantation. The replacement of carmustine with bendamustine (BeEAM) was recently described as a promising alternative in non-Hodgkin lymphoma. The aim of this retrospective study was to compare the BeEAM to the BEAM regimens in MCL patients in the frontline setting.

Sixty and 108 patients were included in the BeEAM and the BEAM groups, respectively. At 3 years, progression-free survival (PFS) was significantly higher in the BeEAM than in the BEAM group (84% [73-96] vs. 63% [51-79];  $p=0.03$ ). However, the overall survival was not statistically different between the two groups ( $p=0.2$ ). According to multivariable analysis, BeEAM regimen remained associated with higher PFS (HR =0.377 95% CI, 0.146-0.970;  $p =0.043$ ). Subgroup analyses in patients treated with prior Rituximab-aracytine induction alone showed that BeEAM improved the PFS compared to the BEAM regimen (84% [71-100] vs. 55% [24-100];  $p=0.04$ ). In patients without rituximab maintenance, there was a trend toward a higher PFS with BeEAM compared to BEAM (80% [65-98] vs. 63 [50-79];  $p=0.07$ ). The treatment related mortality was not increased with the BeEAM regimen.

This retrospective study suggests that the BeEAM regimen is effective and could be considered as an alternative to the BEAM regimen in MCL patients undergoing ASCT.

## Introduction

Mantle cell lymphoma (MCL) accounts for 3% to 6% of all cases of non-Hodgkin lymphoma (NHL). Considered incurable, MCL is characterized by a high risk of relapse responsible for a poor prognosis. Risk stratification with the MCL international prognostic index (MIPI) highlighted the heterogeneity of disease course with an overall survival (OS) of 60 % at 5 years for patient with low-risk MIPI and a median OS of 29 months in patients with high-risk MIPI.<sup>1</sup> For indolent MCL, observation may initially be the appropriate option. For younger symptomatic patients, induction chemotherapy followed by intensification with autologous stem cell transplantation (ASCT) remains the standard of care that significantly increased the progression-free survival (PFS) and overall survival (OS) to 54% and 83% at 3 years respectively.<sup>2</sup> The best induction therapy prior to ASCT remains debated; however, rituximab and cytarabine-based therapy should be considered a priority to reach complete remission (CR) and limit relapse after ASCT.<sup>3,4</sup> In older patients non eligible for intensification, bendamustine plus rituximab or bendamustine in combination with other drugs such as cytarabine has demonstrated an interesting efficacy profile and could be considered a good treatment approach for MCL patients.<sup>5,6,7,8,9,10</sup>

Carmustine (BCNU)-based conditioning regimens, such as the BEAM regimen (carmustine, etoposide, cytarabine and high-dose melphalan), were reported for the first time in 1986.<sup>11,12</sup> Due to its safety and feasibility compared to total body irradiation, BEAM became the standard conditioning regimen prior to ASCT for a large array of lymphoma histology. For several years, few alternatives were suggested to challenge BEAM, but the shortage and unexplained increasing cost of BCNU led physicians to look for alternative drugs.<sup>13</sup>

Preclinical studies demonstrated that bendamustine in association with other purine analogs, such as cytarabine, enhanced *in vitro* cytotoxic effect inducing a phase S blockage and triggering apoptosis.<sup>14,15</sup> More recently, Visani *et al.* assessed the feasibility of bendamustine in combination with the same drugs (BeEAM) as a BCNU replacement for the conditioning regimen in NHL. They reported good drug tolerance, with the exception of grade 3–4 mucositis (26%) and grade 2–4 gastroenteritis (35%), but no increased transplant-related mortality.<sup>16,17</sup> According to the promising results of bendamustine in the treatment of MCL, the synergistic effect of this drug in combination with cytarabine and its feasibility in the BeEAM regimen, we conducted a multicenter retrospective study to assess the efficacy of the BeEAM in comparison to the BEAM regimen as first-line therapy in a homogenous cohort of patients with MCL undergoing ASCT.

## **Methods**

### *Patient enrollment*

The study included patients from 18 to 65 years old who had untreated mantle cell lymphoma (MCL) and were eligible to undergo autologous stem cell transplantation (ASCT). Local expert pathologists established the diagnosis of mantle cell lymphoma according to the applied international classification at the time of diagnosis. We retrospectively recorded MCL patients who received BeEAM conditioning from LYSA centers who accepted to participate in this study from 2014 to 2015. Clinical and biological data were retrieved from each single file and validated by the participating physician. This cohort was compared to a standard cohort of patients who received BEAM conditioning from 2000 to 2008.<sup>18</sup> Clinicians were asked to report clinical data such as age, disease stage, MIPI score, the type of induction chemotherapy and the

disease status before and after ASCT (according to the Cheson's criteria 1999) as complete remission (CR), partial remission (PR) or stable/progressive disease (SD/PD).<sup>19</sup> The use of rituximab maintenance therapy was also reported and local physicians updated patients' outcome at 3 years.

We reported in this work some of the toxicities of the BeEAM regimen (for more data, please refer to the paper of Chantepie et al.<sup>20</sup>). Briefly, acute kidney injury was defined according to KDIGO guidelines as an increase in creatininemia  $> 26.5 \mu\text{mol/L}$ , a creatininemia/initial creatininemia ratio  $>1.5$  or a dialysis requirement. The grade of mucositis and gastrointestinal toxicities were also recorded according to the CTCAE v 4.0. Infectious diseases based on blood culture were noticed. The toxicity of the BEAM regimen was not reported. All patients signed a non-opposition form for the use of their data for the purpose of the study.

#### *Conditioning regimen and supportive care*

According to international practices and considering the day of graft infusion the day 0, the BEAM regimen consisted of BCNU on day -6 ( $300 \text{ mg/m}^2$ ), etoposide daily from day -6 to day -3 ( $100 \text{ mg/m}^2$  every 12 h), cytarabine daily from day -6 to day -3 ( $200 \text{ mg/m}^2$  every 12 h), and melphalan on day -2 ( $140 \text{ mg/m}^2$ ). The BeEAM regimen was similar except that BCNU is replaced by  $200 \text{ mg/m}^2$  bendamustine on day -8 and day -7. G-CSF was administered from day 4 until the neutrophil count was  $> 0.5 \text{ G/L}$ . Others supportive cares were applied according to the centers' practices.

#### *Statistical analyses*

For comparisons of continuous variables (expressed as the median with the interquartile range or range) between groups (BeEAM and BEAM arms), a Student's

*t*-test was used. For categorical variables, a  $\chi^2$  or Fischer's exact test when appropriate was performed.

The endpoints analyzed were progression-free survival (PFS), cumulative incidence of relapse (CIR) and overall survival (OS) after ASCT according to the Cheson's criteria.<sup>19</sup> Univariable analysis with a log rank test was used to compare PFS and OS between groups. Survival curves for PFS and OS were estimated using a Kaplan-Maier method with censoring of the patients lost to follow-up. CIR and nonrelapse mortality (NRM) were assessed using a competing risk methodology considering NRM as a competitive event of relapse. CIR and NRM were estimated using the Kalbfleisch and Prentice approach and were compared in both groups with Gray's test.

A logistic regression was performed for PFS and CIR. A Cox regression model was used to select the best multivariable model for PFS. A Fine and Gray test based on the Bayesian Information Criteria was used to select the best multivariable model for CIR.

Next, we performed a subgroup analyses to determine whether the impact of the conditioning regimen on PFS and CIR was modified by induction chemotherapy (R-aracytine-based regimen or sequencing regimen with R-anthracycline/R-aracytine) or the absence of rituximab maintenance. The results are given with a confidence interval of 95%.

Statistical tests were performed using a 2-tailed  $\alpha$  level of 0.05 and the R software programs (version 3.4.0) with the cmprsk package and coxph function.<sup>21,22</sup>

## Results

### *Patient characteristics*

We identified 60 patients treated with BeEAM and 108 patients treated with BEAM from 26 centers; the median age (range) was 59 (36-70) years and 58 (31-69) years, respectively ( $p=0.045$ ). Characteristics were unbalanced concerning the disease status before transplant, with 49 patients (82%) and 65 patients (60%) in CR in the BeEAM and BEAM groups, respectively. Induction chemotherapy with R-aracytine-based regimen (R-aracytine) alone was administered in 35 patients in the BeEAM (58%) and 22 patients (20%) in the BEAM groups respectively. Whereas, sequencing chemotherapy with R-aracytine and R-anthracycline-based regimen (R-aracytine/R-anthracycline) was administered in 22 patients (35%) in the BeEAM and 68 patients (63%) in the BEAM groups respectively. Furthermore, rituximab maintenance was administered to 34 patients (57%) in the BeEAM group and 4 patients (4%) in the BEAM group. The remaining characteristics of the patients are detailed in Table 1.

### *ASCT procedure and complications with the BeEAM regimen*

The median dosage (range) of bendamustine delivered was 200 (90-200) mg/m<sup>2</sup>/day. Twenty-three patients received a reduced dosage of bendamustine, adapted for renal function, between 90 and 186 mg/m<sup>2</sup>/day on day -8 and day -7. The median dosage of etoposide was 200 (100-200) mg/m<sup>2</sup>/day. Six patients received a reduced dosage between 100 and 150 mg/m<sup>2</sup> per day from day -5 to day -2. The median dosage of cytarabine was 400 (100-400) mg/m<sup>2</sup>/day with 25 patients who received a half dose of cytarabine. The median dosage of melphalan was 140 (62-140) mg/m<sup>2</sup>/day. A reduced dosage of melphalan between 62 and 130 mg/m<sup>2</sup> on day -2 was administered to 7 patients.

Among all patients in the BeEAM group, 28 (46%) developed acute renal failure (ARF), and 19 patients (32%) presented with KDIGO III ARF following the ASCT. Almost all patients presented with grade I to IV mucositis, and 12 patients (20%) presented with grade IV mucositis. Twenty-eight patients (46%) developed a documented septicemia principally due to bacteria from the digestive tract, with enterobacteria in 17 patients (28%) and *Enterococcus* spp. in 2 patients (3%). The remaining patients had infectious diseases due to *Staphylococcus* spp. (3%) and HHV-6 (3%).

#### *ASCT outcome*

In the BeEAM group, 49 patients (82%) were in CR before ASCT. Among these patients, 41 were still in CR (84%), and 8 (16%) relapsed within the 3 years after ASCT. The median time of relapse was 34 (range) (9-36) months. All patients in PR at transplant (n=7; 12%) achieved a CR before rituximab maintenance (100%) and were still alive 3 years after ASCT. Four patients died: 2 from relapse, 1 from septicemia during ASCT procedure and 1 from heart failure after hospital discharge.

In the BEAM group, among the 65 patients in CR (60%) at ASCT, 53 (81%) were still in CR, and 12 (18%) relapsed. Among the 41 patients (38%) in PR, 32 achieved CR (78%), and 9 relapsed (22%) within the 3 years after ASCT. The median time of relapse was 19 (3,5-32) months. Eleven patients died: 6 from relapse, 4 due to ASCT procedure, 1 from secondary malignancy.

#### *Univariable analysis*

For the whole cohort, the 3-year PFS was 73% [95% confidence interval (CI): 65-82]. The PFS was significantly higher in patients in the BeEAM (84% [95% CI: 73-96])



compared to patients in the BEAM group (63% [95% CI: 51-79]); ( $p=0.03$ ). We observed a trend toward a higher PFS in patients with low-risk MIPI (85% [95% CI: 69-100]) compared to patients with intermediate-risk MIPI (68% [68% CI: 48-95]) and high-risk MIPI (56% [95% CI: 37-84]); ( $p=0.07$ ).

The 3-year CIR in the whole cohort was 24% [95% CI: 17-33]. The CIR was positively influenced by the BeEAM regimen. The CIR was 13% [95% CI: 5-24] in the BeEAM group compared to 35% [95% CI: 22-48]); ( $p =0.02$ ) for patients treated with the BEAM regimen. Similarly, we observed a trend toward a lower CIR in patients with low-risk MIPI (15% [95% CI: 3-36]) compared to intermediate-risk MIPI (23% [95% CI: 8-43]) and high-risk MIPI (36% [95% CI: 17-56]); ( $p=0.07$ ).

The 3-year OS in the whole cohort was 88% [95% CI: 82-94]). Only a progressive disease or stable disease status at ASCT influenced negatively OS (50% [95% CI: 12-100]) compared to partial response (91% [95% CI: 80-100]) or complete response (87% [95% CI: 80-94]); ( $p=0.04$ ). Neither bendamustine nor BCNU-based conditioning influenced OS (93% [95% CI: 86-99] vs. 84% [95% CI: 74-94];  $p=0.2$ ) (Table 2, Figure 1).

### *Multivariable analysis*

In the Cox regression model, bendamustine-based conditioning (Hazard ratio (HR) = 0.377, 95% CI: 0.146-0.970;  $p=0.043$ ) and low-risk MIPI (HR = 0.226, 95% CI: 0.061-0.841;  $p=0.027$ ) were associated with a higher PFS.

In the Fine and Gray model, the type of conditioning and MIPI at diagnosis, were selected. Bendamustine-based conditioning was an independent factor with positive impact on the CIR (HR = 0.37, 95% CI: 0.147-0.932;  $p=0.035$ ). A low-risk MIPI was also associated with lower CIR (HR = 0.226, 95% CI: 0.064-0.802;  $p=0.021$ ) (Table 3).

### *Subgroup analysis*

Among patients with R-aracytine induction, we observed higher PFS (84% [95% CI: 71-100] vs. 56% [95% CI: 24-100];  $p=0.04$ ) and a lower CIR (10% [95% CI: 2-24] vs. 44% [95% CI: 2-84];  $p=0.04$ ) in the BeEAM compared to the BEAM group (Figure 2 a-b).

Among patients treated with a sequencing induction of R-aracytine/R-anthracycline we did not observe differences between the BeEAM and the BEAM regimen for PFS (81% [95% CI: 64-100] vs. 66 [95% CI: 52-82];  $p=0.3$ ) and CIR (19% [95% CI: 4-40] vs. 33 [95%: 19-48;];  $p=0.36$ ) (Figure 2 c-d). Neither BeEAM nor BEAM conditioning influenced OS in R-aracytine (94% [CI: 87-100] vs. 98 [76-100];  $p=0.6$ ) or R-aracytine/R-anthracycline subgroups (87% [CI: 72-100] vs. 87% [77-99];  $p=0.9$ ).

We analyzed patients who did not receive rituximab maintenance. We observed a trend toward a higher PFS (80% [95% CI: 65-98] vs. 63 [95% CI: 50-79];  $p=0.07$ ) and lower CIR (14% [95% CI: 4-30] vs. 36% [95% CI: 22-49];  $p=0.06$ ) in the BeEAM compared to the BEAM regimen (Figure 3). There was no difference regarding OS between groups (91% [95% CI: 81-100] vs. 86% [95% CI: 78-95];  $p=0.6$ ).

## **Discussion**

This is the first retrospective study that compared the BeEAM to the BEAM regimen in MCL patients undergoing ASCT in the frontline setting. The results highlight the ability of bendamustine to improve PFS and limit CIR as compared to standard conditioning with BEAM. Although the two cohorts were unbalanced in terms of disease status at transplant and the use of rituximab maintenance, the multivariable analysis showed that the BeEAM regimen remained associated with a higher PFS and lower CIR.

The recent validation of the association of rituximab and aracytine as induction therapy followed by ASCT as the new gold standard explained the unbalance characteristics in our cohort. In sub group analyses, the BeEAM regimen still provides an enhanced benefit in term of PFS and CIR for patients who received previously R-aracytine alone. Curiously this benefit is not significant in patients who received the sequencing regimen of R-aracytine/R-anthracycline as induction therapy. The insufficient number of patients in the BeEAM group could explain the lack of statistical significance in this subgroup.

Due to the recent validation of post-transplant rituximab maintenance and the year of ASCT in the BEAM group, patients who were treated with the BeEAM conditioning received more maintenance rituximab therapy (n=34; 57%) than patients who received the BEAM conditioning (n=4; 4%). Indeed, rituximab maintenance after ASCT was shown to prolong PFS and OS in MCL patients who underwent ASCT.<sup>23</sup> In our cohort, the lack of a long follow-up and the limited number of patients may explain the absence of the beneficial effect of R-maintenance. Nevertheless, the use of BeEAM without rituximab maintenance is not deleterious compared to BEAM regimen. Indeed, PFS is slightly better in the BeEAM than the BEAM group (80% [95% CI: 65-98] vs. 63 [95% CI: 50-79])

Is to note that the OS was similar in both groups and only patients with progressive or stable disease had a significant reduction in OS. This result may be explained by the availability of several second-line therapies, such as ibrutinib, lenalidomide or bortezomib, which considerably improve the duration of survival in MCL patients.<sup>24</sup>

Although the feasibility of BeEAM is clearly accepted,<sup>16,17,25</sup> its toxicity profile was not, as almost all conditioning regimens, prospectively compared to other

conditioning regimen. We recently reported a large retrospective study on the toxicity of this regimen and we did not find an increased transplant related mortality which remained around 3%.<sup>20</sup> In the present study no patients died due to renal toxicity, and the majority of the ARF cases were reversible, as has been previously reported.<sup>16,17,26,27</sup> Identifying factors that indicate patients at risk of ARF such as age over 55 years, a history of previous ARF and the use of concomitant nephrotoxic drugs could stratify patients for ARF risk and adapt supportive care strategy.<sup>20,28</sup> Furthermore, 47% of patients presented with grade III-IV mucositis, which is more frequent than in previous studies on the BEAM regimen.<sup>29,30,31,18</sup> Gastro intestinal toxicity could explain the high rate of septicemia with bacteria from digestive tract but as renal toxicity, it remained manageable and was not associated with increased NRM in our study.

In conclusion, despite a high rate of reversible renal and mucosal toxicities, this retrospective study supports that the BeEAM regimen is safe and effective. It could be considered as an alternative to BEAM regimen in MCL patients in the frontline ASCT setting

### **Authors' contributions**

TH and GD designed and wrote the manuscript. TH and RM performed all statistical analyses. All authors reviewed and approved the manuscript.

### **Disclosure statement**

The authors declare that they have no competing interests.

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## Tables and Figures

Table 1. Patients' characteristics

Table 2. Univariable analysis

Table 3. Multivariable analysis

Figure 1. Univariable analysis

Figure 2. Subgroup analysis according to induction regimen

Figure 3. Subgroup analysis in patients without rituximab maintenance

## Tables

Patients	BeEAM (n=60)	BEAM (n=108)	<i>p</i> *
Age, median, range	59 (36-70)	58 (31-69)	<b>0.045</b>
Sex (Male/Female)	47/13	91/17	
MIPI score, n (%)			0.36
Low	18 (30)	21 (20)	
Intermediate	19 (32)	11 (10)	
High	14 (23)	13 (12)	
Missing data	9 (15)	63 (58)	
Induction chemotherapy, n (%)			<b>0.0001</b>
R-aracytine <sup>¶</sup>	35 (58)	22 (20)	
R-aracytine <sup>¶</sup> /R-anthracycline	22 (35)	68 (63)	
Missing data	3 (5)	18 (17)	
Disease status before ASCT <sup>§</sup> , n (%)			<b>0.001</b>
CR	49 (82)	65 (60)	
PR	7 (12)	41 (38)	
SD/PD	0 (0)	2 (2)	
Missing data	4 (6)	0 (0)	
Time to ANC >0.5x10 <sup>9</sup> /mL, median (range)	11 (7-77)	12 (8-99)	0.744
Rituximab maintenance, n (%)			<b>0.0001</b>
Yes	34 (57)	4 (4)	
No	20 (33)	104 (96)	
Missing data	6 (10)	0 (0)	
Year of transplantation, n (%)			<b>0.0001</b>
2000 to 2005	0 (0)	23 (21)	
2006 to 2010	0 (0)	85 (79)	
2011 to 2015	60 (100)	0 (0)	
Follow-up duration in months, median (range)	37 (1-49)	36 (1-154)	

**Table 1. Patients' characteristics**

BeEAM: Bendamustine, etoposide, cytarabine, melphalan; BEAM: BCNU, etoposide, cytarabine, melphalan; MIPI: Mantle cell lymphoma international prognostic index; R: Rituximab; ASCT: Autologous stem cell transplantation; CR: Complete remission; PR: Partial remission; SD/PD: Stable disease/progressive disease; ANC: Absolute neutrophil count.

<sup>¶</sup> R-aracytine-based regimen

<sup>§</sup> According to Cheson's criteria

\*  $\chi^2$  or Fischer's exact test, when appropriate, was performed to compare the BEAM group to the BeEAM group.

	Patients	3-year OS (CI)	<i>p</i> *	3-year PFS (CI)	<i>p</i> *	3-year CIR (CI)	<i>p</i> **
Whole cohort	168	88% (82-94)		73% (65-82)		24% (17-33)	
Age			0.1		0.2		0.21
< 58 yrs	81	93% (86-100)		81% (71-93)		18% (9-30)	
> 58 yrs	87	84% (76-93)		67% (55-81)		29% (18-40)	
Sex			0.6		0.5		0.46
Male	138	88% (82-94)		72% (63-83)		25% (16-34)	
Female	30	90% (77-100)		72% (56-100)		23% (6-47)	
MIPI score			0.2		<b>0.07</b>		<b>0.07</b>
Low	39	100%		85% (69-100)		15% (3-36)	
Intermediate	30	93% (84-100)		68% (48-95)		23% (8-43)	
High	27	86% (73-100)		56% (37-84)		36% (17-56)	
Induction chemotherapy			0.8		0.4		0.41
R-aracytine¶	57	93% (86-99)		71% (54-92)		17% (7-31)	
R- aracytine¶/R- anthracycline	90	88% (80-97)		71% (60-84)		29%(18-41)	
Disease status before ASCT§			<b>0.04</b>		0.2		0.62
CR	114	87% (80-94)		74% (65-86)		22% (14-32)	
PR	48	91% (80-100)		70% (54-90)		30% (14-48)	
SD/PD	2	50% (12-100)		NA.		NA.	
Conditioning			0.2		<b>0.03</b>		<b>0.02</b>
BEAM	108	84% (74-94)		63% (51-79)		35% (22-48)	
BeEAM	60	93% (86-99)		84% (73-96)		13% (5-24)	
Rituximab maintenance							
Yes	38	89% (76-100)	0.7	85% (71-100)	0.2	15% (3-33)	0.24
No	124	88% (81-94)		66% (55-78)		28% (19-38)	

**Table 2. Univariable analysis**

OS: Overall survival; PFS: Progression-free survival; CIR: Cumulative incidence of relapse; CI: Confidence interval; MIPI: Mantle cell lymphoma International prognostic index; CR: Complete remission; PR: Partial response; SD/PD: Stable disease/progressive disease; ASCT: Autologous stem cell transplantation; BEAM: BCNU, etoposide, cytarabine, melphalan; BeEAM: Bendamustine, etoposide, cytarabine, melphalan.

¶ R-aracytine-based regimen

§ According to Cheson's criteria

\* Log Rank test; \*\* Gray's test

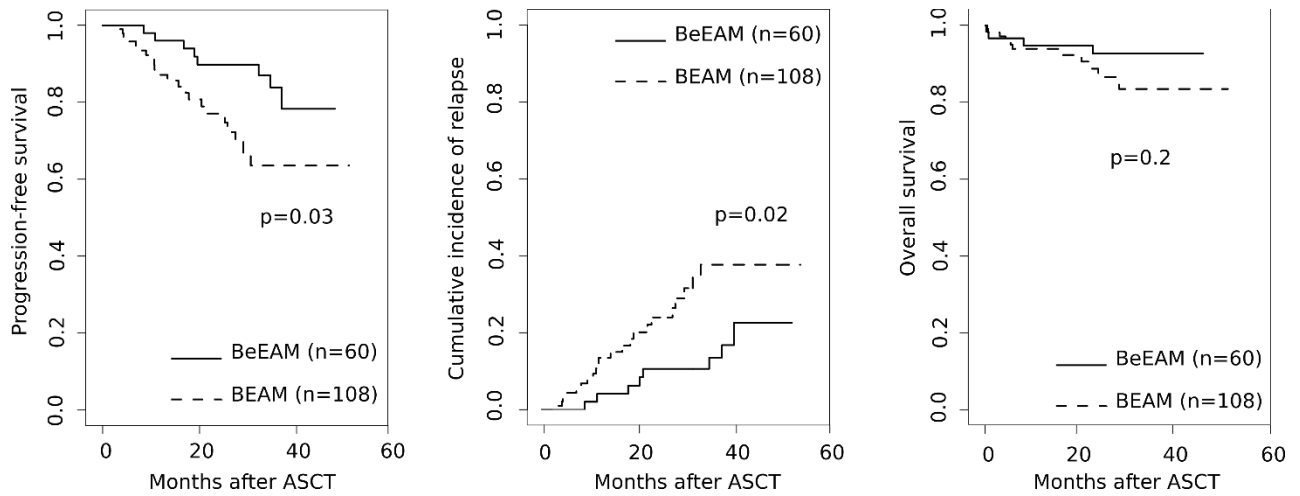
	PFS			CIR		
	HR	CI	<i>p</i> *	HR	CI	<i>p</i> **
MIPI						
Low	0.226	0.061-0.841	<b>0.027</b>	0.226	0.064-0.802	<b>0.021</b>
Int	0.562	0.199-1.585	0.276	0.549	0.188-1.599	0.270
High	1			1		
Conditioning						
BEAM	1			1		
BeEAM	0.377	0.146-0.970	<b>0.043</b>	0.370	0.147-0.932	<b>0.035</b>

**Table 3. Multivariable analysis**

HR: Hazard ratio; CI: Confidence interval; PFS: Progression-free survival; CIR: Cumulative incidence of relapse; MIPI: Mantle cell lymphoma international prognostic index; BEAM: BCNU, etoposide, cytarabine, melphalan; BeEAM: Bendamustine, etoposide, cytarabine, melphalan.

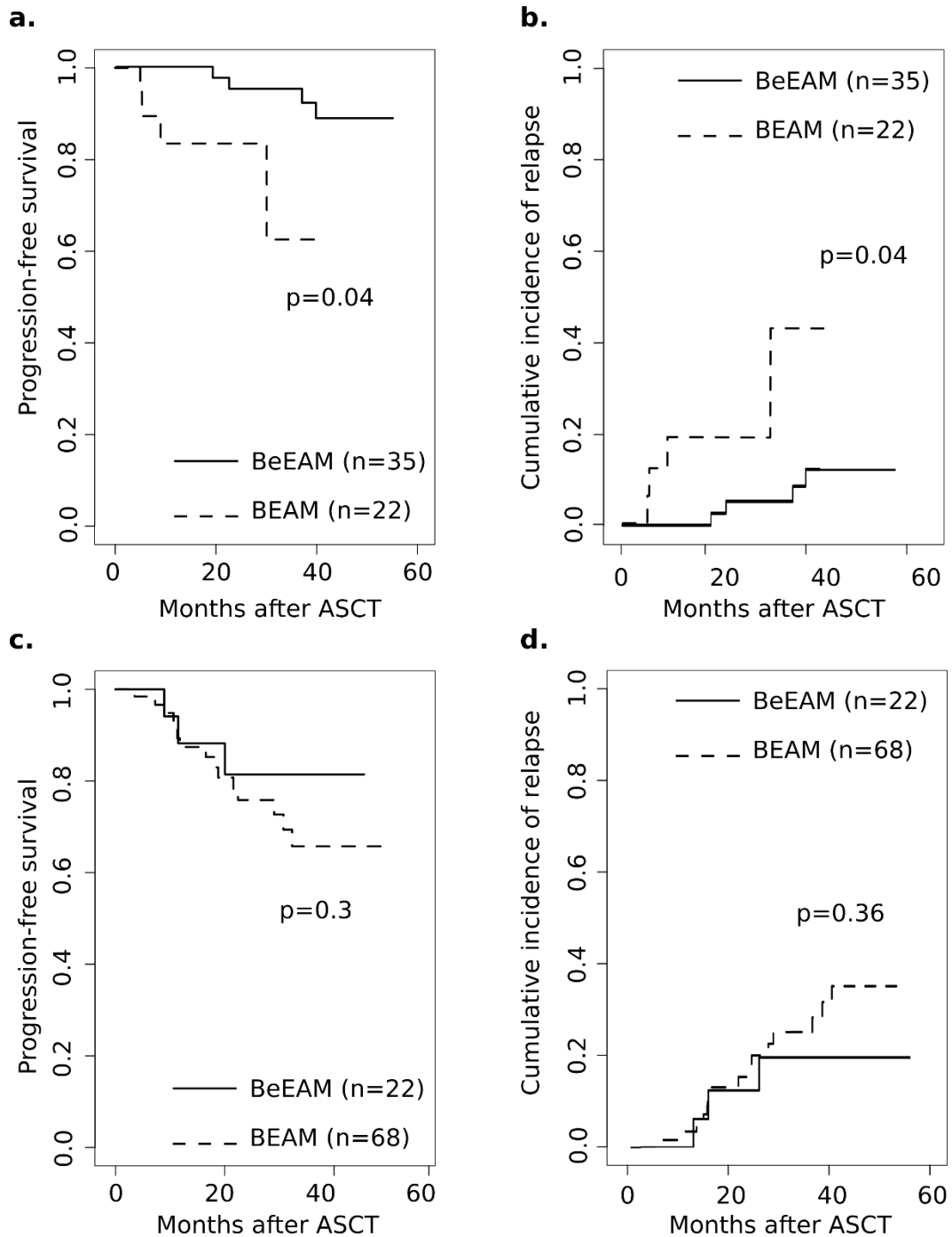
\* Cox regression model; \*\* Fine and Gray model

## Figures



### Figure 1. Univariable analysis

BEAM: BCNU, etoposide, cytarabine, melphalan; BeEAM: Bendamustine, etoposide, cytarabine, melphalan.  $p$  values were determined with the log-rank test for progression-free survival and overall survival and with a Gray's test for the cumulative incidence of relapse.

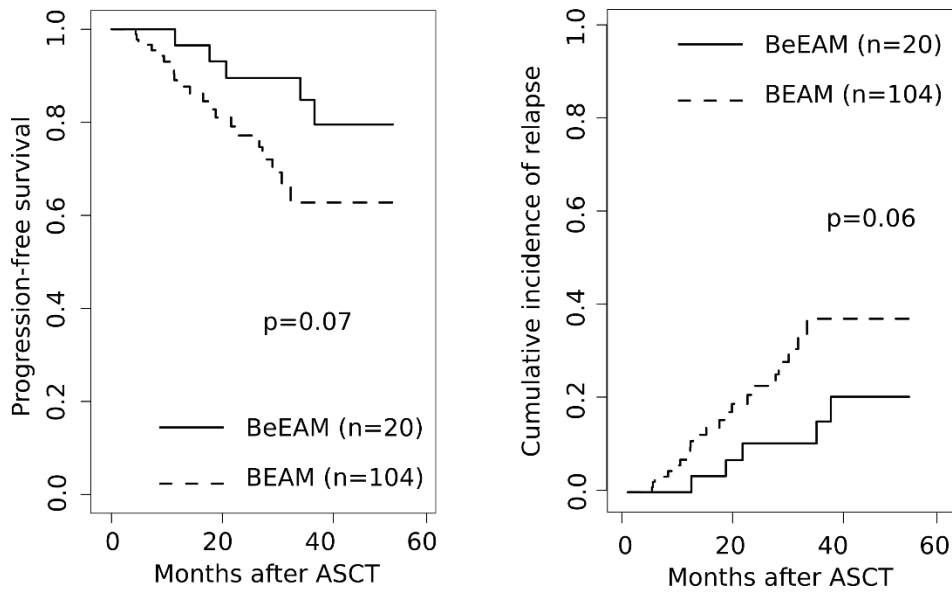


**Figure 2. Subgroup analysis according to induction regimen**

Progression-free survival and cumulative incidence of relapse according to the induction therapy regimen; a-b: R-aracytine-based regimen alone; c-d: R-aracytine/R-anthracycline regimen.

BEAM: BCNU, etoposide, cytarabine, melphalan; BeEAM: Bendamustine, etoposide, cytarabine, melphalan.  $p$  values were determined using a log-rank test for progression-free survival and Gray's test for cumulative incidence of relapse.





**Figure 3. Subgroup analysis in patients without rituximab maintenance**

Progression-free survival and cumulative incidence of relapse in patients without rituximab maintenance.

BEAM: BCNU, etoposide, cytarabine, melphalan; BeEAM: Bendamustine, etoposide, cytarabine, melphalan. *p* values were determined using a log-rank test for progression-free survival and Gray's test for cumulative incidence of relapse.

## Conclusion

Il s'agit du premier travail rétrospectif comparant le conditionnement par BeEAM au conditionnement de référence BEAM chez les patients atteints d'un MCL traités en première ligne.

Nos résultats mettent en évidence une efficacité similaire voire supérieure du BeEAM par rapport au BEAM en terme de PFS et de CIR sans modification de la survie globale à 3 ans. On note toutefois une augmentation de la toxicité rénale et muqueuse par rapport aux données déjà publiées sur le BEAM sans augmentation de la mortalité liée à la procédure de greffe qui reste estimée à 3%. Ces données sont cohérentes avec les travaux déjà publiés sur l'efficacité de la bendamustine et de son association à l'aracytine dans le traitement des MCL.

Ces données suggèrent enfin que la Bendamustine offre une alternative intéressante à la carmustine dans le conditionnement d'autogreffe des patients atteints d'un MCL en première ligne.

## Annexes

### Annexe 1.



#### C.L.E.R.S

Comité Local d'Éthique de la Recherche en Santé

CHU de CAEN Normandie – Université de CAEN Normandie

Caen, le 23 Mai 2019

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**Objet :** Avis favorable

Cher collègue,

Réponse du questionnaire	
ID de la réponse	405
Date de soumission	2019-03-05 18:57:55
Avis du CLERS	FAVORABLE
Demandeur [Nom]	hueso
Demandeur [Prénom]	thomas
Demandeur [e-mail]	
Titre de l'étude	Benda-EAM versus BEAM in patients with mantle cell lymphoma undergoing autologous stem cell transplantation: a multicenter retrospective study of the Lymphoma study association (LYSA).

Cordialement

Le Président du CLERS

**Rappels :** Nous vous rappelons que votre traitement de données doit être en conformité avec le Règlement Européen du 27 avril 2016 (UE-2016/679) relatif à la protection des données des personnes physiques à l'égard du traitement des données à caractère personnel. Les participants doivent avoir été informé et pouvoir s'opposer à l'utilisation de leurs données de santé pour ce travail de recherche.

En aucun cas vous n'êtes autorisé à sortir du CHU des données médicales nominatives, que ce soit par mail, via un circuit non sécurisé ou par transfert sur une clé USB. Le traitement et l'utilisation de ces données engagent votre responsabilité.



**Bendamustine-EAM versus BEAM regimen in patients with mantle cell lymphoma undergoing autologous stem cell transplantation in the frontline setting: a multicenter retrospective study from Lymphoma Study Association (LYSA) centers.**

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Manuscript ID	AJH-19-0981
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	13-Aug-2019
Complete List of Authors:	Hueso, Thomas; University Hospital Centre Caen, Clinical Hematology Gastinne, Thomas; University Hospital Centre Nantes, Clinical Hematology Garciaz, Sylvain; Paoli-Calmettes Institute, Clinical Hematology Tchernonog, Emmanuelle; University Hospital Centre Montpellier, Clinical Hematology Delette, Caroline; University Hospital Centre Amiens-Picardie, Clinical Hematology Casasnovas, Olivier; University Hospital Centre Dijon, Clinical Hematology; Inserm UMR 1231 Durot, Eric; University Hospital Centre Reims, Clinical Hematology Houot, Roch; University Hospital Centre Rennes, Clinical Hematology; Inserm UMR 1236 Tessoulin, Benoit; University Hospital Centre Nantes, Clinical Hematology TOURNILHAC, OLIVIER; University Hospital Centre Clermont-Ferrand, Clinical Hematology Malak, Sandra; Hopital Rene Huguenin, Clinical Hematology Gyan, Emmanuel; Regional University Hospital Centre Tours, Clinical Hematology; Inserm UMR 1415 Fornecker, Luc-Matthieu; University Hospital Centre Strasbourg, Clinical Hematology Abraham, Julie; University Hospital Centre of Limoges, Clinical Hematology Delapierre, Baptiste; University Hospital Centre Caen, Clinical Hematology Peyrade, Frédéric; Antoine-Lacassagne Centre, Clinical Hematology Lemal, Richard; University Hospital Centre Clermont-Ferrand, Clinical Hematology Gressin, Remy; University Hospital Centre Grenoble Alpes, Clinical Hematology Borel, Cecile; IUCT Oncopole Morello, Remy; University Hospital Centre Caen, Biostatistic and Clinical Research Chantepie, Sylvain; University Hospital Centre Caen, Clinical Hematology Bouabdallah, Krmo; University Hospital Centre Bordeaux, Clinical Hematology

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	Hematology Ibrahim, Ahmad; Makassed General Hospital bouabdallah, reda; Paoli-Calmettes Institute, Clinical Hematology LeGouill, Steven; University Hospital Centre Nantes, Clinical Hematology; CRCINA Damaj, Gandhi; University Hospital Centre Caen, Clinical Hematology; University of Caen Normandy
Keywords:	Bendamustine, conditioning, autologous stem cell transplantation, mantle cell lymphoma





« Par délibération de son Conseil en date du 10 Novembre 1972, l'Université n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ou mémoires. Ces opinions doivent être considérées comme propres à leurs auteurs ».

VU, le Président de Thèse

VU, le Doyen de la Faculté

VU et permis d'imprimer  
en référence à la délibération  
du Conseil d'Université  
en date du 14 Décembre 1973

Pour le Président  
de l'Université de CAEN et P.O

Le Doyen



NOM ET PRENOM DE L'AUTEUR : HUESO THOMAS

TITRE DE LA THESE : Bendamustine-étoposide-cytarabine-melphalan (BeEAM) versus. Carmustine-étoposide-cytarabine-melphalan (BEAM) chez les patients atteints de lymphome à cellules du manteau traités par autogreffe en première ligne : Étude comparative rétrospective multicentrique des centres du Lymphoma Study Association (LYSA)

RESUME DE LA THESE EN FRANÇAIS : L'association de la carmustine, étoposide, cytarabine et du melphalan (BEAM) constitue le conditionnement de référence avant autogreffe de cellules souches hématopoïétiques chez les patients atteints d'un lymphome à cellules du manteau (MCL). Le remplacement de la carmustine par la bendamustine (BeEAM) a été récemment décrit et proposé comme une alternative intéressante dans le conditionnement des lymphomes non-Hodgkinien. L'objectif de ce travail était de comparer le conditionnement de référence par BEAM au conditionnement par BeEAM chez les patients atteints d'un MCL autogreffés en première ligne.

Soixante patients furent inclus dans le groupe BeEAM et 108 patients dans le groupe BEAM. A 3 ans en analyse univariée, la survie sans progression (PFS) était significativement meilleure dans le groupe BeEAM comparé au groupe BEAM (84% [73-96] vs. 63% [51-79];  $p=0,03$ ). La survie globale était similaire dans les deux groupes ( $p=0,2$ ). En analyse multivariée, le conditionnement par BeEAM restait associé à une meilleure PFS (HR=0.377 95% CI, 0.146-0.970;  $p=0.043$ ). L'analyse en sous-groupe a mis en évidence chez les patients traités initialement par une association basée sur le Rituximab et l'aracytine, une meilleurs PFS chez les patients qui ont bénéficié du BeEAM comparé aux patients avec BEAM (84% [71-100] vs. 55% [24-100];  $p=0.04$ ). Chez les patients qui n'ont pas eu de maintenance par Rituximab, la PFS semblait meilleure chez les patient du groupe BeEAM comparé au patients du groupe BEAM (80% [65-98] vs. 63 [50-79];  $p=0.07$ ).

Cette étude rétrospective suggère que le conditionnement par BeEAM représente une alternative intéressante au conditionnement par BEAM chez les patients atteints d'un MCL autogreffés en première ligne.

MOTS CLES : Bendamustine; conditionnement; autogreffe de cellules souches hématopoïétiques; lymphome à cellules du manteau

TITRE DE LA THESE EN ANGLAIS : Bendamustine-EAM versus BEAM regimen in patients with mantle cell lymphoma undergoing autologous stem cell transplantation in the frontline setting: a multicenter retrospective study from Lymphoma Study Association (LYSA) centers.

RESUME DE LA THESE EN ANGLAIS: The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) as conditioning regimen prior to autologous stem-cell transplantation (ASCT) remains the standard of care for patients with mantle cell lymphoma (MCL) who are eligible for transplantation. The replacement of carmustine with bendamustine (BeEAM) was recently described as a promising alternative in non-Hodgkin lymphoma. The aim of this retrospective study was to compare the BeEAM to the BEAM regimens in MCL patients in the frontline setting. Sixty and 108 patients were included in the BeEAM and the BEAM groups, respectively. At 3 years, progression-free survival (PFS) was significantly higher in the BeEAM than in the BEAM group (84% [73-96] vs. 63% [51-79];  $p=0.03$ ). However, the overall survival was not statistically different between the two groups ( $p=0.2$ ). According to multivariable analysis, BeEAM regimen remained associated with a higher PFS (HR=0.377 95% CI, 0.146-0.970;  $p=0.043$ ). Subgroup analyses in patients treated with prior R-aracytine induction alone showed that BeEAM improved the PFS compared to the BEAM regimen (84% [71-100] vs. 55% [24-100];  $p=0.04$ ). In patients without rituximab maintenance, there was a trend toward a higher PFS with BeEAM compared to BEAM (80% [65-98] vs. 63 [50-79];  $p=0.07$ ). The treatment related mortality was not increased with the BeEAM regimen.

This retrospective study suggests that the BeEAM regimen is effective and could be considered as an alternative to the BEAM regimen in MCL patients undergoing ASCT.

KEY WORDS : Bendamustine; conditioning; autologous stem cell transplantation; mantle cell lymphoma