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THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en HEMATOLOGIE.

Comparaison de la toxicité selon la posologie d'Etoposide et de Cytarabine dans le traitement des lymphomes par « BEAM »

Toxicity profile according to etoposide and cytarabine dosing in patients with lymphoma receiving autologous stem cell transplantation following BEAM conditioning

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Sous la direction de M. ORVAIN Corentin

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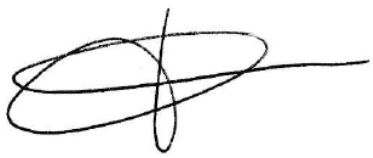

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Liste des abréviations

aaIPI	age adjusted Index Pronostic International
aNHL	aggressive Non Hodgkin Lymphoma
AutoSCT	Autologous Stem Cell Transplantation
B-BEAM	iodine-131 tositumomab (Bexxar), BEAM
BCNU	Carmustine
BEAC	Carmustine, Etoposide, Cytarabine, Cyclophosphamide
BEAM	Carmustine (BCNU), Etoposide, Cytarabine (Aracytine), Melphalan
BeEAM	Bendamustine, Etoposide, Cytarabine, Melphalan
BMT	Bone Marrow Transplant
BuCyE / BuCyVP16	Busulfan, Cyclophosphamide, Etoposide
BuEM	Busulfan, Etoposide, Melphalan
BuMelTT	Busulfan, Melphalan, Thiotepa
CBV	Cyclophosphamide, Carmustine, Etoposide
CEB	Cyclophosphamide, Etoposide, Carmustine
CEEP	Cyclophosphamide, Epirubicine, Vindesine, Prednisone
CLV	Cyclophosphamide, Lomustine, Etoposide
CR	Complete Response
CT-scan	Computed Tomography scan
CY-E-TBI	Cyclophosphamide, Etoposide, Total Body Irradiation
Cy-TBI	Cyclophosphamide, Total Body Irradiation
DLBCL	Diffuse Large B Cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
FEAM	Fotemustine, Etoposide, Cytarabine, Melphalan
FL	Follicular Lymphoma
HDC	High Dose Chemotherapy
HL	Hodgkin Lymphoma
ICU	Intensive Care Unit
iNHL	indolent Non Hodgkin Lymphoma
IP	In Patient
LACE	Lomustine, Cytarabine, Cyclophosphamide, Etoposide
LDH	Lactate Dehydrogenase
LEAM	Lomustine, Etoposide, Cytarabine, Melphalan
mBEAM	modified-BEAM
MC	Methotrexate, Cytarabine
MCL	Mantle Cell Lymphome
MITO/MEL	Mitoxantrone, Melphalan
NHL	Non Hodgkin Lymphoma
ns	non significant
OP	Out Patient
OS	Overall Survival
PBST	peripheral-blood stem cell transplant
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival

PR	Partial Response
R-BEAM	Rituximab, BEAM
TBI	Total Body Irradiation
TECAM	Thiotepa, Etoposide, Cyclophosphamide, Cytarabine, Melphalan
TMC	Thiotepa, Carboplatin, Mitoxantrone
TRM	Therapy Related Mortality
ULN	Upper Limit of Normal
V-BEAM	Bortezomib, BEAM
Z-BEAM	Ibritumomab tiuxétan (Zevalin), BEAM

Plan

MISE EN SITUATION

Les lymphomes sont des pathologies cancéreuses des organes lymphoïdes. Il en existe deux grandes catégories, les lymphomes Hodgkiniens (LH) et les lymphomes non Hodgkiniens (LNH) (1,2). Les LNH sont le plus fréquemment de la lignée B (2). Leur incidence a augmenté dans les années 1990 puis s'est stabilisée, avec une estimation de 72580 nouveaux cas aux Etats Unis en 2016 (2). L'incidence du LH est 8 fois moins importante, avec une estimation de 9050 nouveaux cas en 2015 (3). Le traitement de première ligne de ces pathologies repose sur une chimiothérapie dès lors qu'il s'agit d'un LH, d'un LNH agressif ou d'un LNH de bas grade présentant des critères de traitement (1–3).

Les patients atteints de lymphome réfractaire ou en rechute après une 1ère ligne sont éligibles à une intensification thérapeutique avec autogreffe depuis les années 1990, proposée par Philip et al. en 1995 ou encore par Linch et al. en 1993, appuyée par l'étude de Milpied et al. en 2004 (4–6). Ce traitement a également été validé pour les LNH avec facteurs d'agressivité dès la première ligne (7). Plusieurs schémas de traitement sont possibles dans ce cadre, les principaux étant le conditionnement par BEAM (carmustine, etoposide, cytarabine, melphalan) (5,6), par BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) (4), par CBV (cyclophosphamide, carmustine, etoposide) (7), et par TBI-cyclophosphamide-etoposide (8). Il existe quelques études rétrospectives et très peu d'étude prospectives comparant ces conditionnements. Parmi celles-ci, une étude rétrospective de Salar et al. basée sur des données collectées prospectivement (9) a montré que l'intensification par chimiothérapie exclusive (BEAM, BEAC, CBV) augmentait la survie globale et la survie sans progression par rapport au schéma couplé avec de la radiothérapie (Cyclophosphamide TBI). Puig et al. ont conclu dans leur étude rétrospective comparant BEAM à CBV à une mortalité liée à la procédure et des effets indésirables modestement plus importants avec le CBV (10). Le traitement par

BEAM est donc l'un des traitements les plus utilisés pour intensification thérapeutique des patients atteints de LH et LNH.

Les posologies de chaque produit inclus dans le BEAM ne sont pas consensuelles dans toutes les études (Tableau 1-3). Les doses de carmustine et de melphalan sont néanmoins les mêmes dans les différentes études et respectivement de 300mg/m² et 140mg/m² (Tableau 1-3). En effet, l'augmentation de la carmustine expose au risque de pneumopathie interstitielle et augmente la mortalité liée à la procédure (11). L'augmentation du melphalan expose à un risque de cystite hémorragique lorsque ce produit est associé au cyclophosphamide et au busulfan (conditionnement BuCyMel) (12), mais une étude de phase I montre qu'au sein du BEAM, l'association à un agent cytoprotecteur permettrait son augmentationjusqu'à 260mg/m² sans majoration de ce risque (13).

A contrario, les posologies de la cytarabine et de l'etoposide sont variables dans les études, allant de 100mg/m²/j à 400mg/m²/j (Tableau 1-3). La majorité des études observationnelles évaluant le traitement par BEAM ou celles comparant BEAM à une chimiothérapie non intensive utilisent l'etoposide à 200mg/m²(un tiers d'entre elles), ou regroupent 100-200mg/m² ou 200-400mg/m² (Tableau 1). La cytarabine est utilisée majoritairement à 400mg/m² dans ces études (Tableau 1). Les études comparant BEAM à d'autres conditionnements et celles évaluant des schémas dérivés du BEAM utilisent majoritairement l'etoposide à 200mg/m² et la cytarabine à 400mg/m² (Tableau 2 et 3).

Malgré l'absence de consensus sur la posologie de l'etoposide et de la cytarabine, leurs toxicités ont été décrites. Une étude de Mills et al. compare un traitement par BEAM avec des doses croissances d'etoposide à 200, 400 et 600mg/m²/j associées à de la cytarabine à 400mg/m² (14). Une majoration de la toxicité digestive (mucite et diarrhée) y est observée avec 600mg/m²/j sans augmentation de la réponse post-autogreffe ; il est donc conseillé une dose maximale d'etoposide à 400mg/m².

Dans leur étude, Milpied et al (5) ont montré que l'association chimiothérapie et intensification par BEAM est supérieur à une chimiothérapie seule en première ligne pour les lymphomes avec critères d'agressivité. Depuis cette étude, la majorité des patients traités par chimiothérapie d'intensification par BEAM reçoivent une dose d'etoposide et de cytarabine à 400mg/m²/j pour chaque ("BEAM 400"), à l'exception de ceux jugés fragile par le prescripteur qui reçoivent une dose d'etoposide et de cytarabine à 200mg/m²/j ("BEAM 200").

A notre connaissance, aucune étude n'a évalué la différence de toxicité ou d'efficacité entre les groupes "BEAM 200" et "BEAM 400" de manière directe. Nous avons donc réalisé cette étude dans ce but.

Les objectifs du travail sont :

- Objectif principal : comparer le profil de toxicité des conditionnements par BEAM 200 et 400.
- Objectifs secondaires :
    - Comparer l'efficacité des conditionnements par BEAM 200 et 400 ;
    - Identifier les facteurs associés avec la survie des patients recevant une intensification thérapeutique par BEAM.

Tableau 1. Caractéristiques des études validant le traitement par BEAM

Reference	Outcome	Sample size	Population	Previous treatment (no)	Therapy arms	CR at 3 month	PFS/OS	Toxicities	TRM
Chopra et al. Blood 1993 (17)	BEAM observational	155	R/R HL	Median : 2	Carmustine 300mg/m² Etoposide 100mg/m² (18) 200mg/m² (137) Cytarabine 200mg/m² /j (18) 400mg/m² /j (137) Melphalan 140mg/m²	24%	5-year : 50% / 55%	Neutropenic fever 100% Bacteremia 34% Pneumonitis 7% Mucositis (grade 4) 7% Enterocolitis 3%	10%
Gaspard et al. CCP 1988 (18)	BEAM observational	26	NHL 73%, HL 7%, ALL 12%, thymoma 8%	Median : 2.7	Carmustine 300mg/m² Etoposide 100mg/m² (14) 200mg/m² (12) Cytarabine 200mg/m² /j Melphalan 140mg/m²	61%	2-year : 53% / -	Nausea 38% Mucositis 46% Diarrhea 27% Bacteremia 38%	0%
Cortelazzo et al. BJH 1997 (49)	MACOP-B 12weeks vs MACOP-B 8 weeks + 1 MAD + BEAM	61 BEAM 60 HDC	DLCL (B or T) first line, advance stage	1	-	83 % (vs 68%)	2-year : 70% (vs 60% : p=0.02) / 73% (vs 62% : p=0.22)	Mucositis 71% Neutropenic fever 38% Bacteremia 21%	3%
Caballero et al. BMT 1997 (19)	BEAM observational	148	R/R NHL 76%, HL 23%	Median : 2	Carmustine 300mg/m² Etoposide 100mg/m² Cytarabine 400mg/m² /j Melphalan 140mg/m²	79%	3-year : 76% / 68%	Mucositis 84% (grade 3-4 30%) Diarrhea 69% Hepatic 32% Infection 87%	5.4%
Linch et al. Lancet 1993 (6)	BEAM vs mini-BEAM Randomized trial	20 BEAM 20 mini-BEAM	R/R HL	Median : 1.8	Carmustine 300mg/m² Etoposide 200mg/m² Cytarabine 400mg/m² /j Melphalan 140mg/m²	40%	3-year : 53% (vs 10% : p=0.02)/ 75% (vs 60% : p=0.32)	-	10%
Milpied et al. NEJM 2004 (5)	CEEPx2-MCx1-BEAM vs CHOP Randomized trial	98 HDC-BEAM 99 CHOP	Ann Arbor III-IV or II Bulky DLBCL 78%, anaplastic 10%, T-cell 5%, other diffuse lymphoma 7%	Frontline	Carmustine 300mg/m² Etoposide 400mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	76% (vs 57%)	5-year : 55% (vs 37% : p=0.03) / 74 % (vs 44% : p=0.001)	-	-
Mills et al. JCO 1995 (20)	BEAM observational	107	R/R NHL	Median : 2	Carmustine 300mg/m² Etoposide 100mg/m² (11) 200mg/m² (96) Cytarabine 200mg/m² /j (11) 400mg/m² /j (96) Melphalan 140mg/m²	41%	5-year : 35% / 41%	Mucositis 73% Diarrhea 82% Neutropenic fever 98% Bacteremia 45% Pneumonitis 17%	1%
Geisler et al. EJH 1998 (48)	BEAM observational	100	NHL (aNHL 47%, iNHL 21%), HL 32%	BMT : < 3 : 24% ≥ 3 : 38% PBST : 38%	Carmustine 300mg/m² Etoposide 200mg/m² Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	4-year : 40% / 45%	Bacteremia 25%	6%
Mills et al. Leuk Lymphoma 1995 (14)	To compare Etoposide 200/400/600mg/m² retrospective	90	NHL (aNHL 35%, iNHL 1%), HL 64%	1 : 32% ≥ 2 : 68%	Carmustine 300mg/m² Etoposide 200mg/m² (40) 400mg/m² (37) 600mg/m² (13) Cytarabine 400mg/m² /j Melphalan 140mg/m²	65%	1-year : 67-72-85%	Mucositis (≥ grade 2) 65% (200) vs 85% (600) Diarrhea 80% (200) vs 100% (600) Nausea 32% Neutropenic fever 99%	6%

Tableau 1. Caractéristiques des études validant le traitement par BEAM (suite)

Gribben et al. Blood 1989 (36)	BEAM observational	44	refractory HL	Median : 2	Carmustine 300mg/m² Etoposide 100-200mg/m² Cytarabine 200-400mg/m² /j Melphalan 140mg/m²	34%	4-year : - / 70%	Bacteremia 40% (200) vs 69% (600) Neutropenic fever 88%	4.5%
Argiris et al. Ann Oncol 2000 (44)	BEAM with PBST observational	40	R/R HL	Median : 2	Carmustine 300mg/m² Etoposide 400mg/m²/j Cytarabine 200mg/m² /j Melphalan 140mg/m²	92%	3-year : 69% / 77%	Severe toxicity : Mucositis 25% Diarrhea 17% Nausea/vomiting 32% Neutropenic fever 67% Pneumonitis 15%	2.5%
Martin et al. Leuk Lymphoma 2015 (22)	Outcome in elderly observational	73	R/R or high risk NHL (DLBCL 57%, FL 10%, MCL 17%, other 16%)	1 : 36% ≥ 2 : 64%	Carmustine 300mg/m² Etoposide 200mg/m²/j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	2-year : 67.2% / 78.5%	Neutropenic fever 98% Septic shock 6.8% Mucositis 88% Diarrhea ≥grade 3 : 2.7%	2.7%
Martin et al. BMT 2004 (50)	BEAM vs escaladed BEAM retrospective	131 (67 BEAM, 64 escaladed BEAM)	NHL (aNHL 38%, iNHL 22%), HL 40%	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m²/j (51%) 400mg/m²/j (49%) Cytarabine 400mg/m² /j Melphalan 140mg/m²	70%	5-year : 60% / 68%	≥ grade 3 Mucositis 27% (200), 50% (400) : p=0.006 Diarrhea 9% (both) Infection 7.5% (both)	-
Phillips et al. BBMT 2011 (13)	BEAM with dose escalation of melphalan Phase I	28	NHL (DLBCL 47%, other 21%), HL 32%	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m²/j Cytarabine 400mg/m² /j Melphalan 140/160/180/200/220/240/260mg/m²	-	5-year : 30% / 53%	Mucositis 96% -	-
Reid et al. Cancer Med 2016 (42)	Inpatient vs Outpatient retrospective	49 IP 58 OP	NHL (aNHL 36%, iNHL 36%), HL 19%, other 9%	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m² Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	2-year (IP vs OP) : 60% vs 70% (p=0.07) / 80% vs 90% (p=0.02)	Grade 2-3 Nausea 30% Mucositis 20% Diarrhea 30% Neutropenic fever 59% Bacteremia : 6%	-
Rossi et al. BJH 1997 (51)	BEAM Observational (hematological recovery)	63	NHL (iNHL 20%, intermediate or a-NHL 80%)	1 : 54% ≥ 2 : 46%	Carmustine 300mg/m² Etoposide 200mg/m² Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	2-year : 53% / -	-	-

HDC : High Dose Chemotherapy ; **PBST**: peripheral-blood stem cell transplant; **BMT**: Bone Marrow Transplant; **HL** : Hodgkin Lymphoma; **NHL** : Non Hodgkin Lymphoma; **aNHL** : aggressive Non Hodgkin Lymphoma ; **iNHL** : indolent Non Hodgkin Lymphoma ; **FL** : follicular lymphoma ; **MCL** : Mantle Cell Lymphoma ; **TRM** : Therapy Related Mortality ; **IP** : In Patient ; **OP** : Out Patient

Tableau 2. Annexe II. Caracteristics of studies comparing BEAM regimen and other intensification regimen

Reference	Outcome	Sample size	Population	Previous treatment (no)	Therapy arms	CR at 3 month	PFS/OS	Toxicities	TRM
Colita et al. Font Oncol 2019 (41)	BEAM vs LEAM vs CLV retrospective	132 BEAM 48 LEAM 42 CLV	HL 56%, NHL-B 33%, NHL-T 9%, other 2%	1-2 : 52% ≥3 : 48%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	BEAM (vs LEAM vs CLV) 74% (vs 63 vs 75%)	2-year (BEAM vs LEAM vs CLV): 87% (vs 80 vs 70%: p=0.03)/ 92% (vs 88 vs 92%: p=0.6)	Grade 3-4 : Mucositis 42% Digestive 4%	0%
Hueso et al. BMT 2020 (43)	BeEAM vs BEAM retrospective	108 BEAM 60 BeEAM	MCL	Frontline	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	3-year (BeEAM vs BEAM): 63% (vs 84%: p=0.03)/ 84% (vs 93%: p=0.2)	-	1%
Jo et al. Ann Hematol 2007 (52)	BEAC vs BEAM retrospective	28 BEAM 56 BEAC	DLBCL 64%, T cell lymphoma 29%, other 7%	-	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	2-year (BEAM vs BEAC): 62% (vs 32% : p=0.001) / 62% (vs 29% : p=0.003)	Grade ≥ 2 Mucositis 45% Nausea 25% Diarrhea 46% Neutropenic fever 75% Septicemia 3%	7.1%
Kelsey et al. BMT 2020 (53)	BEAM vs LEAM retrospective	650 BEAM 410 LEAM	R/R HL, NHL	-	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	5-year : 49% (vs 54% : p=0.09) / 65% (vs 66%)	-	3%
Liu et al. I.J.Radiation Oncology 2010 (35)	CY-E-TBI vs BEAM retrospective	47 BEAM 26 CY-E-TBI	NHL (aNHL 68%, iNHL 32%)	Median : 3	Carmustine 300mg/m² Etoposide 400mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	5-year : 50.7% (vs 50%: p=0.8) / 64% (vs 54%: p=0.49)	All grades / grade ≥ 3 : Mucositis 93% / 6% Diarrhea 58% / 9% Pneumonitis 2% / 2%	4%
Khattry et al. Int J Hematol 2016 (54)	BEAM vs LACE retrospective	64 BEAM 75 LACE	NHL 37%, HL 63%	≤ 2 : 61% > 2 : 31 % Unknown : 8%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	5-year : 47% (vs 37% : p=0.39) / 47% (vs 46%)	Mucositis 77% Diarrhea : 39%	13%
Kim et al. Leuk Res 2011 (55)	BEAM vs BuCyE retrospective	43 BEAM 22 BuCyE	high risk or R/R NHL (DLBCL 51%, T-cell 39%, other 10%)	1 : 28% ≥2 : 72%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	63% (vs 82% : p=0.59)	Median (month): 16 (vs 11: p=0.62) / 30.6 (vs 22.6: p=0.84)	Grade ≥ 2 : Mucositis 40% Nausea 30% Diarrhea : 40% Neutropenic fever 67% Septicemia 12%	4.3%
Kothari et al. BMT 2016 (56)	BEAM vs LEAM Retrospective	50 BEAM 50 LEAM	R/R DLBCL 40%, FL 28%, HL 32%	-	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	98% (vs 96%)	3-year : 75% / 86%	Mucositis 60% Diarrhea 76%	2%
Marchesi et al. BMT 2019 (40)	BEAM vs FEAM	200 BEAM 164 FEAM	NHL (DLBCL 43.5%, MCL 8%, iNHL 10%, T-cell 11%) HL 27.5%	1 : 15% 2 : 65% ≥3 : 20%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	87% (vs 74.7%)	2-year : 76% (vs 74%: p=0.2)/ 87% (vs 84%: p=0.58)	Mucositis grade ≥ 3 : 30% Documented infection : 63%	-
Olivieri et al. BBMT 2018 (57)	BEAM vs FEAM Retrospective	607 BEAM 431 FEAM	HL 27%, NHL (indolent NHL 15%, DLBCL 30%, MCL 13%, other 15%)	1 : 30% 2 : 56% ≥3 : 14%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	84% (vs 80% : p=0.4)	2-year : 72% (vs 68%: ns) / 84% (vs 83.7%: ns)	All grades / grade ≥ 3 : Mucositis 82% / 31% Nausea 12% / 12% Diarrhea 21% / 21% Neutropenic fever 46%/ 46% Infection 66% / 66%	-
Patir et al. Exp Clin	BEAM vs TECAM Retrospective	72 BEAM 36 TECAM	R/R HL 33%, NHL (DLBCL 36%, MCL	1 : 11% ≥2 : 89%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j	-	2-year : 53% (vs 55.7%: p=0.8) / 67% (vs 56%: p=0.23)	Septicemia 47%	8%

Tableau 2. Annexe II. Caracteristics of studies comparing BEAM regimen and other intensification regimen (suite)

Transplant 2018 (58)			8%, FL 3%, T cell 13%, other 7%)		Melphalan 140mg/m²			
Puig et al. Leuk Lymphoma 2006 (10)	BEAM vs CBV Retrospective	38 BEAM 75 CBV	HL 7%, NHL (DLBCL 45%, MCL 14%, FL 24%, T cell 17%)	1 : 16% 2 : 74% ≥3 : 5%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	-	Mucositis : 34% Gastrointestinal : 16%	5%
Sakellari et al. Leuk Lymphoma 2015 (33)	BEAM vs BuEM Retrospective	87 BEAM 50 BuEM	HL 69%, NHL 31%	1-2 : 42% 3-4 : 44% ≥5 : 14%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	2-year : 63.2% (vs 65.5%: p=0.75)/ 76.7% (vs 79.8%: p=0.69)	All grades / grade ≥ 3 : Mucositis 93% / 6.8% Gastrointestinal 98% /54.5% Liver toxicity : 52%/7% Renal toxicity : 16%/2% Infection : 65%	3%
Saleh et al. Leuk Lymphoma 2017 (59)	BEAM vs BeEAM retrospective	68 BEAM 34 BeEAM	HL 26% , NHL (DLBCL 44%, iNHL 21%, MCL 3%, T-cell 6%)	1 : 35% 2 : 46% 3 : 24%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	78% (vs 85%)	2-year : 75% (vs 75%: ns) / 85% (vs 86%: ns)	Grade ≥ 3 Diarrhea 15% Nausea 19% Mucositis 38% Bacteremia 13%	-
Shi et al. Asia Pac JCO 2017 (60)	BEAM vs CBV vs BEAC retrospective	36 BEAM	DLBCL 64%, T-cell 25%, other 11%	1 : 36% ≥2 : 64%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	5-year : 67% (vs 44 vs 67%: p=0.4)/ 78% (vs 69 vs 82%: p=0.58)	Grade ≥ 2 : Mucositis 47% Nausea 42% Diarrhea 64% Neutropenic fever 58% Documented infection 47%	0%
Singer et al. BBMT 2019 (29)	BEAM vs BuCyVP16 retrospective	269 BEAM 409 BuCyVP16	DLBCL 58%, FL 5%, MCL 24%, other 13%	Median : 2	Carmustine 300mg/m² Etoposide 100mg/m² /j Cytarabine 100mg/m² /j Melphalan 140mg/m²	-	3-year : 59% (vs 54%: p=0.52) / 75% (vs 69%: p=0.11)	Mucositis grade ≥ 3 : 24%	3.3%
Wang et al. BMT 2004 (61)	BEAM vs CEB retrospective	20 BEAM 52 CEB	NHL 79% HL 21%	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	80% (vs 63% : p=0.09)	-	Mucositis 60% Nausea 65% Diarrhea 65% Bacteremia 35%	10%
Yeral et al. Clin Lymphoma Myeloma Leuk 2020 (39)	BEAM vs MITO/MEL retrospective	34 BEAM 108 MITO/MEL	HL	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	3-year : 76.5% (vs 86%: p= 0.93) / 91% (vs 86%: p=0.86)	Neutropenic fever 91% Septicemia 12% Pulmonary 29% Diarrhea grade ≥ 3 9%	0%
Zaucha et al. Leuk Lymphoma 2008 (62)	BEAM vs BuMelTT retrospective	49 BEAM 58 BuMelTT	DLBCL 62%, iNHL 19%, T-cell 15%, other 4%	1 : 51% ≥2 : 49%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	31% (vs 56%)	2-year : 38% (vs 58%: ns) / 50% (vs 65%: ns)	Grade 2 / grade ≥ 3 : Mucositis 80% / 12% Diarrhea 62% / 14% Neutropenic fever 86%	

LEAM : Lomustine, Etoposide, Cytarabine, Melphalan **; CLV :** Cyclophosphamide, Lomustine, Etoposide **; BeEAM :** Bendamustine, Etoposide, Cytarabine, Melphalan **; BEAC :** Carmustine, Etoposide, Cytarabine, Cyclophosphamide **; CY-E-TBI :** Cyclophosphamide, Etoposide, Total Body Irradiation **; LACE :** Lomustine, Cytarabine, Cyclophosphamide, Etoposide **; BuCyE or BuCyVP16 :** Busulfan, Cyclophosphamide, Etoposide **; FEAM :** Fotemustine, Etoposide, Cytarabine, Melphalan **; TECAM :** Thiotepa, Etoposide, Cyclophosphamide, Cytarabine, Melphalan **; CBV :** Cyclophosphamide, Carmustine, Etoposide **; BuEM :** Busulfan, Etoposide, Melphalan **; Cy-TBI :** Cyclophosphamide, Total Body Irradiation **; MITO/MEL :** Mitoxantrone, Melphalan **; CEB :** Cyclophosphamide, Etoposide, Carmustine **; BuMelTT :** Busulfan, Melphalan, Thiotepa **; ns :** non significant

Tableau 3. Caractéristiques des études évaluant les schémas dérivés du BEAM

Reference	Outcome	Sample size	Population	Previous treatment (no)	Therapy arms	CR at 3 month	PFS/OS	Toxicities	TRM
Berger et al. Hematol Oncol 2016 (63)	Z-BEAM vs R-BEAM	11 Z-BEAM 35 R-BEAM	MCL	1 : 59% 2-3 : 41%	Carmustine 300mg/m² Etoposide 300mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	(Z vs R) 100% vs 89%	4-year (Z vs R) : 41 vs 32%(p=0.3) / 71 vs 55%(p=0.28)	Grade 2/3 : Mucositis 28% Colitis 63% Neutropenic fever 87% Pneumonia 19%	0%
Shimoni et al. Cancer 2012 (64)	BEAM vs Z-BEAM prospective	21 BEAM 22 Z-BEAM	R/R DLBCL 99%, PMBL 1%	1-2 : 100%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	97%	2-year (vs Z-BEAM): 37% (vs 59% : p=0.2)/ 62% (vs 91% : p=0.05)	Grade ≥ 3 : Mucositis 43% Hepatic 14%	-
Vose et al. JCO 2013 (65)	R-BEAM vs B-BEAM	113 R-BEAM 111 B-BEAM	DLBCL	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	-	2-year (B vs R): 49% (both) / 60 vs 66% (p=0.3)	Grade ≥ 3 : Mucositis 18% (R) vs 52% (B) (p<0.01) Diarrhea 13% Dyspnea 25%	-
William et al. BBMT 2014 (34)	V-BEAM Phase I/II	42	R/R iNHL, MCL in first CR	Median : 1	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	86%	1-year : 83% / 91%	All grades/grade 3 : Mucositis 59% / 0% Diarrhea 54% / 4% Neutropenic fever 59%/59% Bacteremia 26% / 26%	-
Krishnan et al. BBMT 2017 (66)	Z-BEAM Phase II	116	DLBCL 55%, FL 17%, MCL 28%	Median : 2	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 200mg/m² /j Melphalan 140mg/m²	82%	3-year : 64% / 84%	Mucositis grade ≥ 2 : 28% Diarrhea grade ≥ 2 : 3%	0.9%
Briones et al. Haematologica 2013 (37)	Z-BEAM Phase II	30	R/R DLBCL	Median : 3	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	60%	3-year : 63% / 65%	All grades / grade ≥ 3 : Mucositis 84% / 40% Diarrhea 54% / 10% Neutropenic fever 76%/10% Infection 50% / 6%	6.6%
Chahoud et al. Clin Cancer Res 2018 (67)	R-BEAM, Z-R-BEAM Phase II	73 R-BEAM 40 Z-R-BEAM	R/R DLBCL	Median : 2	Carmustine 300mg/m² Etoposide 400mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	5-year (R vs Z-R): 62 vs 65% (p=0.8) / 73 vs 77% (p=0.65)	-	4%
Ciochetto et al. Ann Hematol 2018 (68)	Z-BEAM vs BEAM Retrospective	37 Z-BEAM 21 BEAM	R/R NHL (iNHL 40%, DLBCL 53%, MCL 7%)	1 : 60% ≥2 : 40%	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	(Z vs BEAM) 71% vs 67%	3-year (Z vs BEAM) : 78 vs 22% (p=0.01)/ 83 vs 22% (p<0.01)	Mucositis grade ≥ 3 : 17%	3%
Galieni BMT 2017 (69)	mBEAM retrospective	44	R/R or high risk NHL (DLBCL 34%, iNHL 29.5%, MCL 4.5%, other 14%), R/R HL 18%	-	Carmustine 300mg/m² Etoposide 200mg/m² /j Cytarabine 2000mg/m²/j Melphalan 140mg/m²	70%	-	All grades / grade ≥ 3 : Mucositis 61% / 14% Diarrhea 46% / 13% Hepatic 27% / 4% Infection 43%	4.5%
Glossmann et al. Ann Hematol 2015 (70)	Tandem TMC followed by BEAM Prospective phase II	25	R/R NHL (DLBCL 36%, MCL 4%, T-cell 20%), HL 40%	Median: 1.6	Carmustine 300mg/m² Etoposide 300mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	28%	1-year : 28% / 40%	Mucositis grade ≥ 3 : 59% Diarrhea grade ≥ 2 : 28% Nausea grade ≥ 3 : 28% Infection 39%	28%
Khouri et al. JCO 2005 (38)	R-BEAM vs BEAM Retrospective	67 R-BEAM 30 BEAM	Relapsed DLBCL	Median: 2	Carmustine 300mg/m² Etoposide 400mg/m² /j Cytarabine 400mg/m² /j Melphalan 140mg/m²	-	2-year (R vs BEAM) : 67 vs 43% / 80 vs 53%	Bacteremia 41%	0%

Z-BEAM : Zevalin, BEAM ; **R-BEAM** : Rituximab, BEAM ; **B-BEAM :** iodine-131 tositumomab, BEAM ; **V-BEAM** : Bortezomib, BEAM; **TMC** : Thiotepa, Carboplatin, Mitoxantrone ; **aaIPI** : age adjusted Index Pronostic International ; **CEEP** : Cyclophosphamide, Epirubicine, Vindesine, Prednisone ; **MC** : Methotrexate, Cytarabine ; **mBEAM** : modified-BEAM

Toxicity profile according to etoposide and cytarabine dosing in patients with lymphoma receiving autologous stem cell transplantation following BEAM conditioning

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ABSTRACT

The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by autologous stem cell transplantation (autoSCT) is a commonly used intensification regimen for relapsed/refractory or in frontline for high-risk lymphomas. Etoposide and cytarabine dosing are not well defined and varies between 100 to 400 mg/m^2 in studies with no direct comparison on tolerability and efficacy. The aim of this retrospective study was to compare toxicity and efficacy in two populations, receiving eihter 400 mg/m^2 ("BEAM 400") or 200 mg/m^2 ("BEAM 200") for both etoposide and cytarabine.

One hundred and ten patients with diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma or Hodgkin lymphoma treated by BEAM regimen were enrolled (41 in the BEAM 200 group and 69 in the BEAM 400 group).

Patients had received a median of 2 lines of chemotherapy prior to intensification by BEAM, most having achieved a complete response before BEAM regimen (78% and 75% in BEAM 200 and BEAM 400 groups respectively). Patients in the BEAM 400 group experienced more toxicity with more hematological (mean duration of neutropenia: 11 vs 7 days, $p<0.001$; duration of neutropenic fever: 6 vs 3 days, $p<0.001$; platelet transfusions: 7 vs 5, $p=0.013$) and digestive toxicity (mucositis: 99% vs 73%, $p<0.001$; but no more diarrhea: 61% vs 54%, $p=0.549$). PFS was lower in the BEAM 200 group ($p=0.047$). OS was lower in BEAM 200 group, although the difference was not statistically significant between the two groups ($p=0.12$).

In conclusion, lower etoposide and cytarabine dosing were associated with less hematological and digestive toxicities even though treatment-related toxicity remained low in both groups. PFS was statistically lower in the BEAM 200 group and OS was lower but this did not reach statistical significance. Larger, multicentric, prospective studies should be carried out to define the optimal dosing.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplantation (autoSCT) is a treatment option for patients with lymphoma, either as first-line therapy (3,4) or after relapse (5-8). This strategy has improved overall and progression free survival (4–7,15,16) with an acceptable toxicity (e.g. a treatment-related mortality from 0 to 10%) (4–7,15,16).

The "BEAM" chemotherapy protocol is a commonly used intensification regimen including the following agents: carmustine (B for BCNU), etoposide (E), cytarabine (A for Aracytine) and melphalan (M) (5,6,17–20). However, the optimal dose for each chemotherapy is still an open question: melphalan and Carmustine are usually administered at 140mg/m^2 and 300mg/m^2 respectively, (5,6,20), but etoposide and cytarabine dosing vary between 100 to 400 mg/m^2 according to different studies. (5,6,17,19,20)

Indeed, the balance between efficacy and toxicity is a crucial endpoint in lymphoma treatment. Main toxic side effects of etoposide are hematologic and digestive, mainly with diarrhea, nausea, mucositis and an increased risk of intestinal bleeding (14). Similar adverse events occur with the use of cytarabine (21). These chemotherapy-induced toxic effects are well-known and increase with the administrated dose (14). On the other hand, previous reports have claimed for efficacy thresholds of these agents. For example, an increased dose of etoposide at 600 mg/m^2 was not associated with an improvement of complete response at three-months post-autoSCT compared with 200 or 400mg/m^2 (64%, 66%, 67% respectively) (14).

A commonly used "BEAM" strategy using both etoposide and cytarabine doses of 400 mg/m^2 has been proposed by Milpied et al. (5). This chemotherapy regimen improved mortality rate in comparison to standard chemotherapy (this is, without autoSCT) (5). Other authors reduced etoposide and cytarabine doses, from 100 to 200 mg/m^2 (17,18,22).

However, to our knowledge, no study compared different etoposide and cytarabine dosing within the "BEAM" intensification chemotherapy protocol. Thus, we hypothesized that a dose reduction from 400 mg/m^2 to 200 mg/m^2 for both etoposide and cytarabine could be associated with a decreased toxicity without reducing efficacy. The aim of this retrospective study was to compare both toxicity and efficacy

in two populations, receiving respectively higher (400mg/m^2) or lower doses (200mg/m^2) of these chemotherapies.

METHODS

1. Study population and setting

We retrospectively analysed the data of 110 consecutive patients with lymphoma receiving a BEAM conditioning regimen followed by autoSCT, hospitalized in the Hematology unit of the Angers University Hospital between January 2012 and December 2019.

Patients had the following histological phenotypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) or Hodgkin lymphoma (HL). They all received BEAM conditioning regimen with both cytarabine and etoposide dosing at either 200 mg/m^2/d (BEAM 200) or 400 mg/m^2/d (BEAM 400). Patients less than 18 years old, with other lymphoma histology, receiving other conditioning regimen or undergoing a second autoSCT or a tandem autoSCT followed by allogenic transplantation were excluded from the study.

Intensification chemotherapy was conducted according to the BEAM procedure including the following four agents: carmustine 300 mg/m² at day 7 before transplantation, both cytarabine and etoposide 200 ou 400 mg/m²/d (according to the BEAM 200 or BEAM 400 regimen) from day 6 to day 3, and melphalan 140mg/m² at day 2 before autologous stem cell reinjection (e.g., day 0) (5,22).

For all patients, graft was composed of peripheral blood progenitor cell (PBPC), obtained by apheresis after stimulation by a G-CSF agent (5 µg/kg per 12 hours) during 5 days.(24) An anti-infectious prophylaxis by valaciclovir and pentamidine aerosol was provided during the hospital stay for each patient.

This study was conducted in accordance with the principles of the Declaration of Helsinki. All patients receiving autoSCT in our institution gave their informed consent. This study was approved by the local transparency (Commission Nationale de l'Informatique et des Libertés, France #ar20-0124v0) and ethic (Angers University Hospital #2021-002) boards.

2. Data collection

Data available in this study were obtained retrospectively, based on a standardized clinical report of chemotherapy toxicity and autologous stem cell transplantation procedure outcomes. These data were reported as soon as conditioning regimen was initiated. Thus, the following patients characteristics were obtained: gender, age, time from diagnosis, general symptoms defined by a loss of weight >10% within the last 6 months, fever or sudation (25), and performance status (26). Disease-related data were also analyzed: histologic phenotype (1), Ann Arbor stage (27), serum LDH level, number of chemotherapy lines prior to autoSCT, refractory disease (defined by the persistence of CT-scan signs at the end of treatment or a relapse within 6 months), Sorror score before autoSCT (28) and response to chemotherapy before autoSCT. The number of re-injected peripheral CD34+ was also reported.

3. Endpoints

Chemotherapy-induced toxicity was defined by any adverse event following conditioning regimen. Hematologic toxicity was defined by neutropenia (neutrophils count <500 mm^3, neutropenia duration and febrile neutropenia), anemia (requirement for red blood cell (RBC) transfusion and duration) or thrombopenia (requirement for platelet transfusion and duration). Infections were considered as clinically relevant if the patient presented sepsis signs associated with a positive microbiologic samples obtained from blood, urines, sputum or feces (e.g. C. difficile toxins)(29). Anti-microbial agents' administration and its duration were also obtained. Digestive toxicity was reported if the patient experienced oral mucositis (and requirement of an opioid therapy) (30) and diarrhea (30). The need for an enteral or parenteral nutrition and weight loss were also reported.

Response to treatment was evaluated 3 months after autoSCT, based on CT-scan or PET-scan according to Cheson criteria (31). Progression Free Survival (PFS) and Overall Survival (OS) were reported. Hospital and intensive care length of stay following the procedure were obtained. Relapse and allogenic stem cell therapy after autoSCT were also reported. Therapy-related mortality (TRM) was defined as death occurring in the absence of progressive cancer (100 days after the procedure) (32).

4. Statistical analysis

Results are expressed as medians [25th-75th quartiles] for quantitative data, and as numbers (%) for qualitative data. Normal distribution of results was assessed for each variable by a D'Agostino and Pearson's test. Comparisons between the BEAM 200 and BEAM 400 groups were performed by using a Mann and Whitney U-test or a Student's t-test as appropriate for quantitative data, and a Chi-square test for qualitative data. Univariable and multivariable Cox regression analysis was performed to identify parameters associated with progression free survival and overall survival. Survival analyses were performed after 2 years of follow-up (n = 110). OS and PFS data were analyzed with a Kaplan-Meier estimator model. All tests were two-sided, and a p value <0.05 was considered as statistically significant. Data analyses were provided by using Prism (GraphPad Prism v 9.2, La Jolla, CA, USA).

RESULTS

1. Patients' characteristics

In this retrospective study, 110 patients were enrolled: 41 patients in the BEAM 200 group, and 69 in the BEAM 400 one. Main characteristics of the patients are reported in Table I. Patients were older in the BEAM 200 than in the BEAM 400 group (62 [58-65] vs. 48 [40-56], respectively, p<0.001), with a lower prevalence of the Hodgkin lymphoma phenotype (4 (10%) vs. 18 (26%), p=0.038). Other characteristics were similar between the two groups (Table I). The initial histology of DLBCL and prognostic scores during chemotherapy prior to the BEAM regimen are reported in Appendix I and II.

Of note, patients had received 2 [1-2] lines of chemotherapy prior to intensification by BEAM protocol, 2 [1-2] in the BEAM 200 and 2 [1-2] in the BEAM 400 groups (p=0.778). The BEAM therapy was used at frontline for 40 patients (36%) in the study population, 15 (37%) and 25 (37%) in the BEAM 200 and BEAM 400 groups respectively (p =0.970), including all but four patients with MCL. Most patients achieved a complete response prior to autoSCT (32 (78%) vs. 52 (75%), respectively in the BEAM 200 and BEAM 400 groups, (p=0.784), whereas 3 patients (3%) received the BEAM protocol in a progressive disease situation (all in the BEAM 400 group) (Table I).

2. BEAM regimen-related toxicities

All patients enrolled in this study experienced neutropenia and thrombopenia following the BEAM protocol, whichever cytarabine and etoposide doses (Table II). However, hematologic toxicity was more important in the BEAM 400 group regarding either neutropenia duration (mean of 7 vs 11 days and median of 9 [7-10] vs. 9 [9-11] days in the BEAM 200 and BEAM 400 groups, respectively, p<0.001)

and neutropenic fever duration (3 [2-6] vs 6 [4-10] days, p<0.001), and requirement for platelet transfusion (5 [3-7] vs. 7 [4-11], p=0.013) (Table II).

In association with the increased duration of neutropenic fever, patients in the BEAM 400 group received longer antibiotic treatments (9 [9-14] vs. 13 [10-18] days in the BEAM 200 and BEAM 400 groups, respectively, p <0.001) and required more frequently an antifungal therapy (8 (20%) vs. 37 (54%), p<0.001) (Table II). Of note, the prevalence of documented infections did not differ significantly between the two groups: 17 (41%) vs. 35 (51%), p =0.430 (Table II). 11 (27%) and 24 (35%) patients had at least one bacteriemia in the BEAM 200 and BEAM 400 groups respectively (p=0.407).

Digestive toxicity was also increased, with a higher prevalence of mucositis (30 (73%) vs. 68 (99%), p <0.001) and an increased opioid exposure (15 (37%) vs. 58 (94%), p <0.001) (Table II). Patients lost 1.0 [-1.0 – 3.5] kg in the BEAM 200 group, vs. 3.0 [1.0-6.0] kg in the BEAM 400 group (p=0.002) (Table II). In-hospital mortality was 2% (2 patients (5%) in the BEAM 200 group vs 0 in the BEAM 400 group, p=0.141).

3. Efficacity analysis

After a median follow up of 83.7 months, there was no significant difference in hospital or intensive care unit length of stay (Table III). Relapse occurred with a higher prevalence in the BEAM 200 group (13 (32%) vs 12 (17%) patients respectively, p=0.102), albeit this result was not statistically significant (Table III). Three months post-autoSCT response to treatment was not significantly different between the two study groups (Figure 1) as most patients were in complete response (36 (88%) vs 64 (93%) in the BEAM 200 and BEAM 400 groups, respectively (p=0.490). PFS was lower in the BEAM 200 group (Figure 2, p=0.047). Median PFS was 105 month in the BEAM 200 group and not reach in the BEAM 400 group (Figure 2). OS is also lower in the BEAM 200 group but the difference was not statistically significant (Figure 2, p=0.120). Median OS were not reach in the two groups. For information, the 2-year PFS in BEAM 200 and BEAM 400 groups were 68% and 82% respectively

(p=0.097, Figure 2, Table III) and the 2-year OS in BEAM 200 and BEAM 400 groups were 90% and 95% respectively (p=0.242, Figure 2, Table III).

To account for potential confounding factors in reporting PFS and OS between the two groups, we performed an univariable and multivariable analysis of potential factors associated with PFS and OS using a Cox regression model. The number of previous lines of treatment, the primary refractory status, and response prior to BEAM conditioning were associated with PFS. After including age and type of BEAM conditioning to these variables, only the primary refractory status and response prior to BEAM conditioning were significantly associated with PFS (Table IV). No variable was significantly associated with OS (*data not shown*).

PFS and OS according to histology lymphoma are reported in Appendix III and IV.

DISCUSSION

High dose chemotherapy followed by autoSCT is the mainstay of lymphoma treatment, either as first-line consolidation therapy in specific lymphoma subtypes (MCL) or after salvage chemotherapy in the relapse setting. Whereas the BEAM conditioning regimen is the most frequently used, it is not known how etoposide and cytarabine dosing influence toxicity and outcome. The main findings of this study could be summarized as follows: (1) hematologic toxicity decreases with etoposide and cytarabine dose reduction, (2) shortened duration of neutropenic fever, infectious risk and exposure to antibiotic and antifungal agents, (3) digestive toxicity, with a lower prevalence of mucositis and a reduced need for opioid therapy, is reduced with the BEAM 200 regimen, (4) no significant difference in 3-month response to treatment but PFS lower in the BEAM 200 group without a significant difference in OS.

This study is, to our knowledge the first to assess toxicity between two etoposide and cytarabine dosing regimens during BEAM intensification chemotherapy in patients with lymphoma. Hematologic and digestive toxicities were more important with BEAM 400 in our study. Neutropenia duration (mean of 11 days vs 7 with BEAM 200) and neutropenic fever duration (median of 6 vs 3 days in BEAM 200 group) were longer with BEAM 400. In a study conducted by Liu et al. using both etoposide and cytarabine doses of 400 mg/m^2, median neutropenia duration was reported at 10 days and neutropenic fever was observed in 81% of patients (35). We found a prevalence of mucositis in 99% of patients receiving BEAM 400 and 73% of those receiving BEAM 200. These results are consistant with previous studies (22,33,34, 35). In our study, the treatment-related mortality was 2%, close to the 0 to 10% rates found in the literature (17,20,36–38).

If toxicity decreases in the BEAM 200 group, this should be balanced with the preliminary efficacy data presented in this study. Survival data are better in the BEAM 400 group with a significant improvement in PFS and non-significant improvement in OS. Interestingly, previously published studies using a BEAM 200 chemotherapy protocol led to results close to ours (22,33,39,40). In a population of 200 patients treated by BEAM regimen, Marchesi et al. found a three-months complete response of 87% (40). 2-year PFS reached 63 to 85%, similar to our 68% rate, and OS 77 to 90% whereas our 2-year OS is 90% in the BEAM 200 group (22,33,39,40). Conversely, survival data are much higher in our study

than in previous reports based on a BEAM 400 regimen: complete response was obtained in 76% of patients in the study by Milpied et al. (5) compared with 92.8% in our study, PFS reached 43 to 60% (83% in ours) and OS 53 to 82% (95% in ours) (5,35,38). These differences can be explained by the relative older age of the studies investigating this chemotherapy regimen, especially in comparison to these based on a "BEAM 200" protocol. Interestingly, most recent studies based on a "mixed" dose schema with etoposide 200 mg/m^2 and cytarabine 400 mg/m^2 found results closer to ours, with a 2-year PFS reaching 70 to 87%, and an OS 90 to 95% (41–43). This confirms that autoSCT after BEAM conditioning is very effective in some aggressive lymphoma subtypes as consolidation therapy during first-line treatment or in the relapse setting.

It is important to note the rapid and constant changes in lymphoma treatment. Intensification chemotherapy followed by autoSCT progressively became a gold-standard in lymphomas in first or second line therapy (4–7,15,16). However, emerging therapeutic options may challenge this strategy: chimeric antigen receptor T- or NK-cells (45,46) and bispecific immunotherapies (47) are currently investigated in this indication and may deeply change standards in the next years.

There are several limitations to this study. First, due to the monocentric, limited sample size, our findings should be generalized with caution, albeit it is similar to other previously published cohorts in this field (5,14,43,48,49). Second, the heterogeneity of our population is another important concern, although we tried to limit this bias by considering only patients with the most prevalent lymphoma phenotypes (1) as it was done in other studies. (14,19,48,50) Third, this is a retrospective study, exposing to several bias, even if the amount of loss to follow-up remained low (4%) and the standardized report of chemotherapy-induced toxicities also enhanced the quality of our data. Fourth, there is an indication bias since prescribers prefered BEAM 200 for elderly or most vulnerable patients. Fifth, patients received various chemotherapy regimens before enrollment; to limit this bias, we chose to limit the enrollment period from 2012 to 2019, allowing to select only patients having received an anti-CD20 therapy during the first line, and to avoid CAR-T cells- or bispecific antibodies-based therapies. Sixth, the inclusion period extending from 2012 to 2019, some patients had a limited follow-up of two years.

CONCLUSION

We confirm the efficacy of autoSCT following BEAM conditioning in different groups of patients with lymphoma. Lower etoposide and cytarabine dosing was associated with less hematological and digestive toxicities even though treatment-related toxicity remained low in both groups. PFS was statistically lower in the BEAM 200 group and OS appeared as lower, but this did not reach statistical significance. Larger, multicentric, prospective studies should be carried out to define the optimal dosing.

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LISTE DES FIGURES

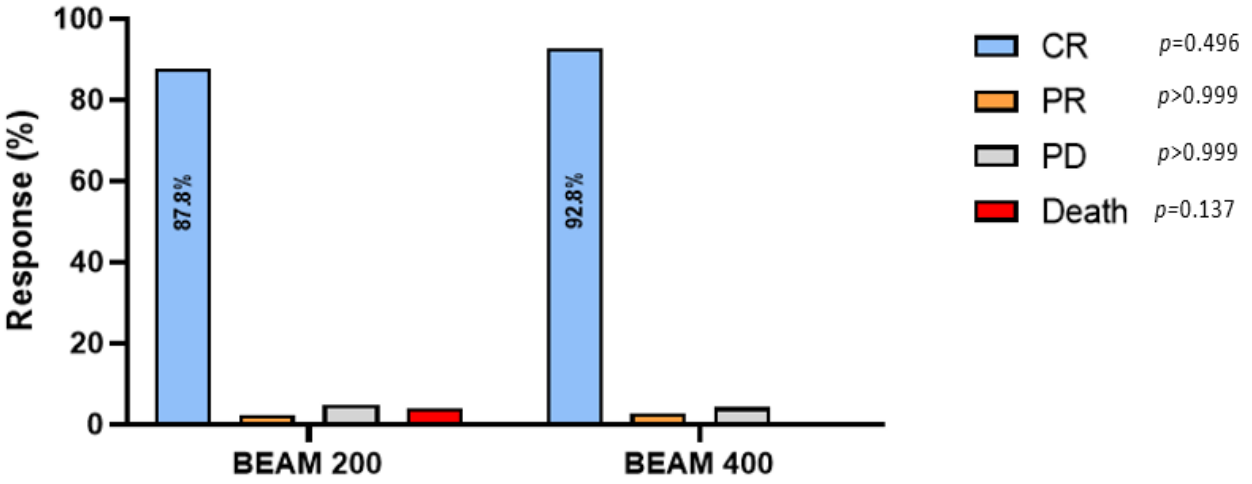


Figure 1. Response at 3-month post-transplant
CR : complete response ; PR : partial response ; PD : progressive disease

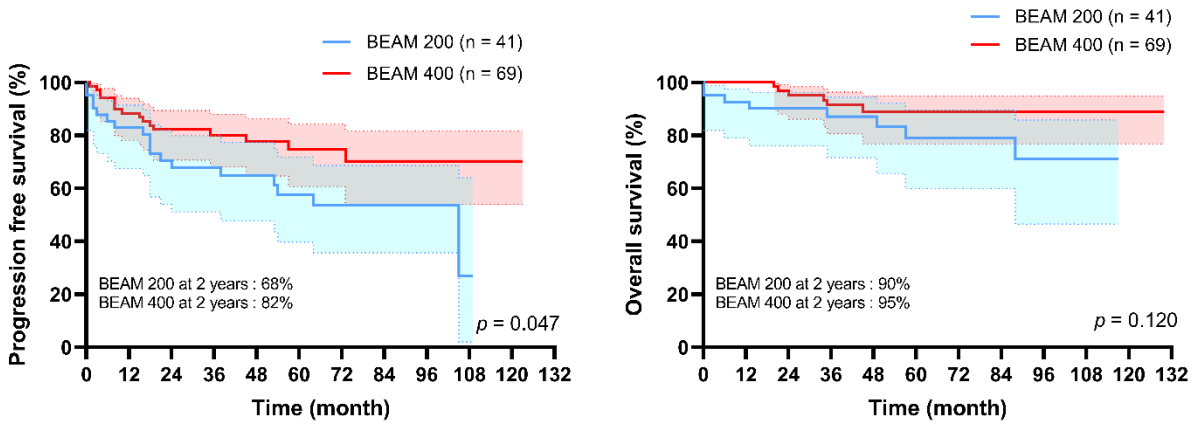


Figure 2. Kaplan-Meier analysis of (A) progression-free survival (PFS) and (B) overall survival with 95% CI

LISTE DES TABLEAUX

Table I. Patients and disease's main characteristics.

	Total n = 110	**BEAM 200 n = 41**	**BEAM 400 n = 69**	***p value***
Male, n (%)	71 (65)	27 (66)	44 (64)	*0.825*
Age at autoSCT, years	55 [46-61]	62 [58-65]	48 [40-56]	***<0.001***
Systemic symptoms, n (%)	30 (27)	14 (34)	16 (23)	*0.212*
Performance status, n (%)				
0-1	91 (83)	34 (83)	57 (83)	*0.966*
≥ 2	14 (13)	7 (17)	7 (10)	*0.291*
Unknown	5 (4)	0	5 (7)	*0.077*
Delay between diagnosis and autoSCT,	13 [6-35]	15 [6-52]	13 [6-32]	*0.701*
Underlying disease, n (%)				
Follicular lymphoma	17 (15)	6 (15)	11 (16)	*0.854*
Mantle cell lymphoma	39 (36)	17 (41)	22 (32)	*0.309*
Hodgkin lymphoma	22 (20)	4 (10)	18 (26)	***0.038***
DLBCL, %	32 (29)	14 (34)	18 (26)	*0.368*
Primary	20 (62)	9 (64)	11 (61)	*0.429*
Secondary	12 (38)	5 (36)	7 (39)	*0.429*
Ann Arbor stage before autoSCT , %				
1	1 (10)	0	1 (1)	*0.438*
2	16 (15)	4 (10)	12 (17)	*0.272*
3	15 (14)	7 (17)	8 (12)	*0.418*
4	78 (71)	30 (73)	48 (70)	*0.687*
Serum LDH level > ULN, n (%)	52 (47)	21 (51)	31 (45)	*0.522*
Regimens of chemotherapy prior to autoSCT, n (%)				
1	40 (36)	15 (37)	25 (37)	*0.970*
2	48 (44)	17 (41)	31 (45)	*0.723*
3	20 (18)	8 (20)	12 (17)	*0.780*
4-5	2 (2)	1 (2)	1 (1)	*0.707*
Refractory lymphoma, n (%)	29 (26)	9 (22)	20 (29)	*0.418*
Sorror score before autoSCT, n (%)				
0	85 (77)	28 (68)	57 (83)	*0.083*
1-2	20 (18)	11 (27)	9 (13)	*0.069*
≥3	5 (5)	2 (5)	3 (4)	*0.897*
Response before autoSCT, n (%)				
Complete response	84 (76)	32 (78)	52 (75)	*0.748*
Partial response	22 (20)	9 (22)	13 (19)	*0.693*
Stable disease	1 (1)	0 (0)	1 (1)	*0.438*
Progressive disease	3 (3)	0 (0)	3 (5)	*0.175*
$CD34^+$ cells reinjection, $x10^6.kg^{-1}$	4 [3-6]	4 [3-5]	5 [3-7]	*0.111*

AutoSCT: autologous stem cell transplantation. DLCBL: Diffuse Large Cell B Lymphoma. LDH: Lactate DesHydrogenase.

Table II. Chemotherapy-induced toxicity in the study population

	Total n = 110	BEAM 200 n = 41	BEAM 400 n = 69	*p value*
Hematologic toxicity				
Neutropenia, n (%)	110 (100)	41 (100)	69 (100)	*>0.999*
Duration, days	9 [8-10]	9 [7-10]	9 [9-11]	***<0.001***
Neutropenic fever, n (%)	108 (98)	40 (97)	68 (99)	*>0.999*
Fever duration, days	5 [3-9]	3 [2-6]	6 [4-10]	***<0.001***
Significant anemia, n (%)	84 (76)	30 (73)	54 (78)	*0.643*
Duration, days	2 [1-8]	1 [1-8]	4 [1-7]	*0.911*
Need for RBC transfusions, n (%)	99 (90)	36 (88)	63 (91)	*0.743*
Number of RBC transfusions, n	4 [2-5]	4 [2-4]	4 [2-6]	*0.363*
Significant thrombopenia, n (%)	105 (95)	40 (97)	65 (94)	*0.649*
Duration, days	9 [7-12]	8 [6-10]	9 [7-13]	*0.087*
Need for Platelet transfusions, n (%)	110 (100)	41 (100)	69 (100)	*>0.999*
Number of platelet transfusion, n	6 [4-10]	5 [3-7]	7 [4-11]	***0.013***
Infections				
Documented infection, n (%)	52 (47)	17 (41)	35 (51)	*0.430*
Antibiotics administration, n (%)	108 (98)	40 (97)	68 (99)	*>0.999*
Antibiotics administration, days	12 [9-16]	9 [9-14]	13 [10-18]	***<0.001***
Antifungal treatment, n (%)	45 (41)	8 (20)	37 (54)	***<0.001***
Antifungal treatment, days	6 [4-7]	5 [4-17]	6 [4-7]	*0.866*
Digestive toxicity				
Mucositis, n (%)	98 (89)	30 (73)	68 (99)	***<0.001***
Morphinic treatment, n (%)	73 (66)	15 (37)	58 (94)	***<0.001***
Morphinic treatment, days	8 [6-10]	7 [7-9]	8 [6-10]	*0.675*
Nutrition supply, n (%)	109 (99)	40 (97)	69 (100)	*0.372*
Parentral, n (%)	106 (96)	39 (95)	67 (97)	*0.627*
Enteral, n (%)	3 (3)	1 (2)	2 (3)	*>0.999*
Duration, days	11 [9-13]	10 [8-12]	11 [9-13]	*0.102*
Diarrhea, n (%)	64 (58)	22 (54)	42 (61)	*0.549*
Duration of treatment, days	6 [3-9]	6 [3-10]	6 [3-8]	*0.491*
Loss of weight, kg	2.2 [0-5]	1 [-1-3.5]	3 [1-5.7]	***0.002***

Table III. Main study's outcomes.

	Total n = 110	**BEAM 200 n = 41**	**BEAM 400 n = 69**	***p value***
Hospital stay				
Hospital lenght of stay, days	24[22-27]	23 [22-28]	24 [23-28]	*0.138*
Need for ICU hospitalization, n (%)	6 (5)	3 (7)	3 (4)	*0.669*
ICU lenght of stay, days	9 [4-15]	3 [3-9]	11 [8-16]	*0.600*
In-hospital mortality, n (%)	2 (2)	2 (5)	0	*0.141*
Post-autoSCT outcome				
Relapse, n (%)	25 (23)	13 (32)	12 (17)	*0.102*
Time from autoSCT to relapse, months	16 [6.5-23.2]	18 [12-46]	15 [8-31]	*0.412*
Need for allogenic SCT, n (%)	12 (11)	3 (7)	9 (13)	*0.529*
2-years outcome, n (%)				
Overall survival	94	90	95	*0.242*
Progression-free survival	77	68	82	*0.097*
Death due to disease progression	10 (9)	5 (12)	5 (7)	*0.496*
Death related to autoSCT	2 (2)	2 (5)	0	*0.137*

AutoSCT: autologous stem cell transplantation, ICU: intensive care unit, SCT: stem cell transplantation.

Table IV. Univariable and multivariable analysis for PFS

	Univariable analysis		**Multivariable analysis**	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Female gender	1.4 (0.7 - 2.8)	0.4		
Age at autoSCT	1 (1 - 1.1)	0.32	1 (1 - 1.1)	0.17
HCT-CI				
0	Ref.			
1 - 2	0.9 (0.3 - 2.3)	0.82		
> 3	0.6 (0.1 - 4.4)	0.61		
Lymphoma subtype at autoSCT				
Hodgkin lymphoma	0.7 (0.2 - 1.9)	0.43		
MCL	0.8 (0.4 - 1.7)	0.6		
Follicular lymphoma	2.1 (0.9 - 5)	0.08	1.4 (.5 - 4.3)	0.53
DLBCL	1 (0.5 - 2.2)	0.99		
Prior treatment lines	1.5 (1 - 2.1)	**0.05**	1.1 (.7 - 1.9)	0.64
First line	Ref.			
First relapse	2 (0.8 - 5)	0.14		
Second relapse or more	2.9 (1.1 - 7.9)	**0.03**		
Primary refractory	2.5 (1.2 - 5.3)	**0.01**	2.9 (1.2 - 7.1)	**0.02**
Response before autoSCT				
CR	Ref.		Ref.	
PR	1.6 (0.7 - 3.8)	0.29	1.3 (.5 - 3.3)	0.55
SD/PD	20 (6 - 68)	**<0.001**	23 (6.1 - 89)	**<0.001**
BEAM 400 conditioning	0.6 (0.3 - 1.2)	0.14	0.6 (0.2 - 1.7)	0.36

TABLE DES MATIERES

APPENDIX

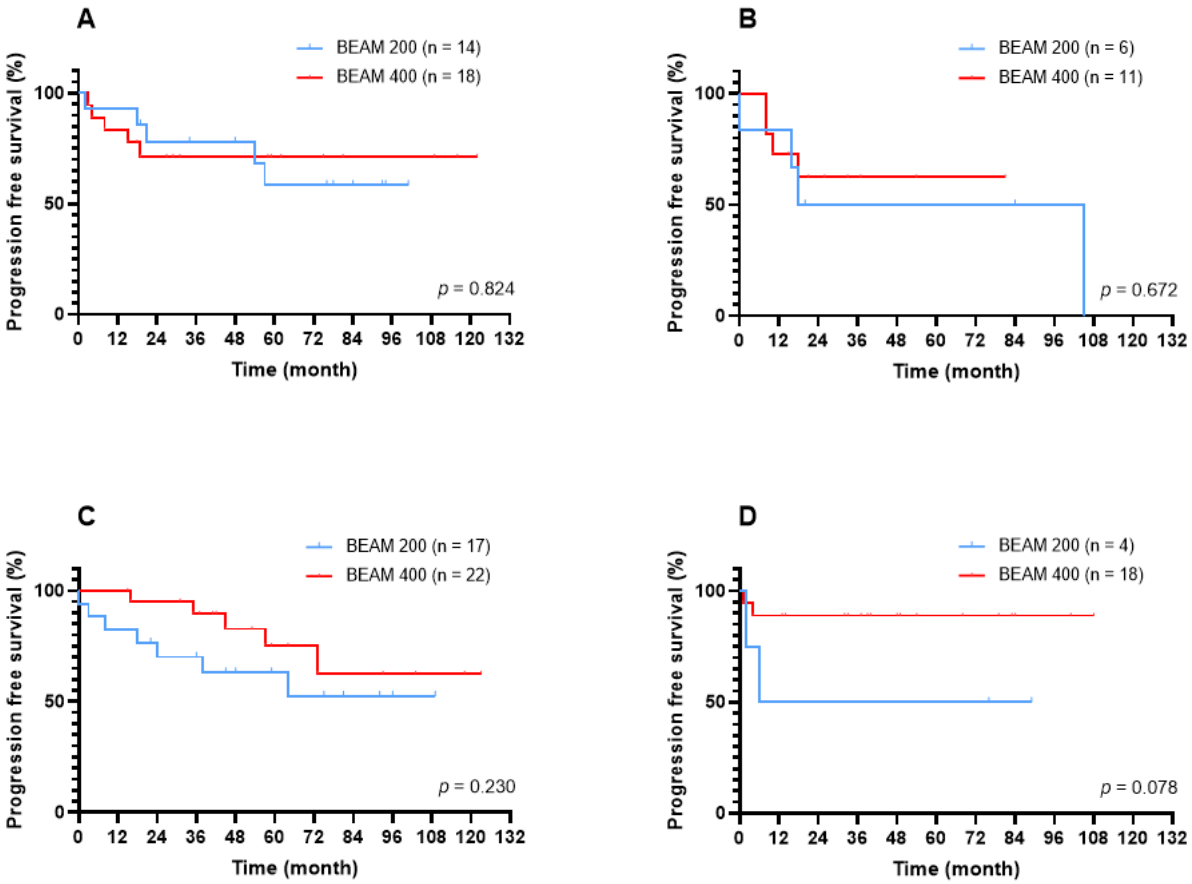
Appendix I. Initial histology of DLBCL

	BEAM 200	BEAM 400	*p value*
Primary DLBCL	9	11	*0.429*
Transformed FL	2	3	*0.897*
Transformed MCL	2	1	*0.275*
Transformed MALT	0	1	*0.438*
Transformed WM	0	1	*0.438*
Transformed CLL	1	0	*0.192*
Transformed Poppema lymphoma	0	1	*0.438*

Appendix II. Pronostic score at last chemotherapy before autoSCT

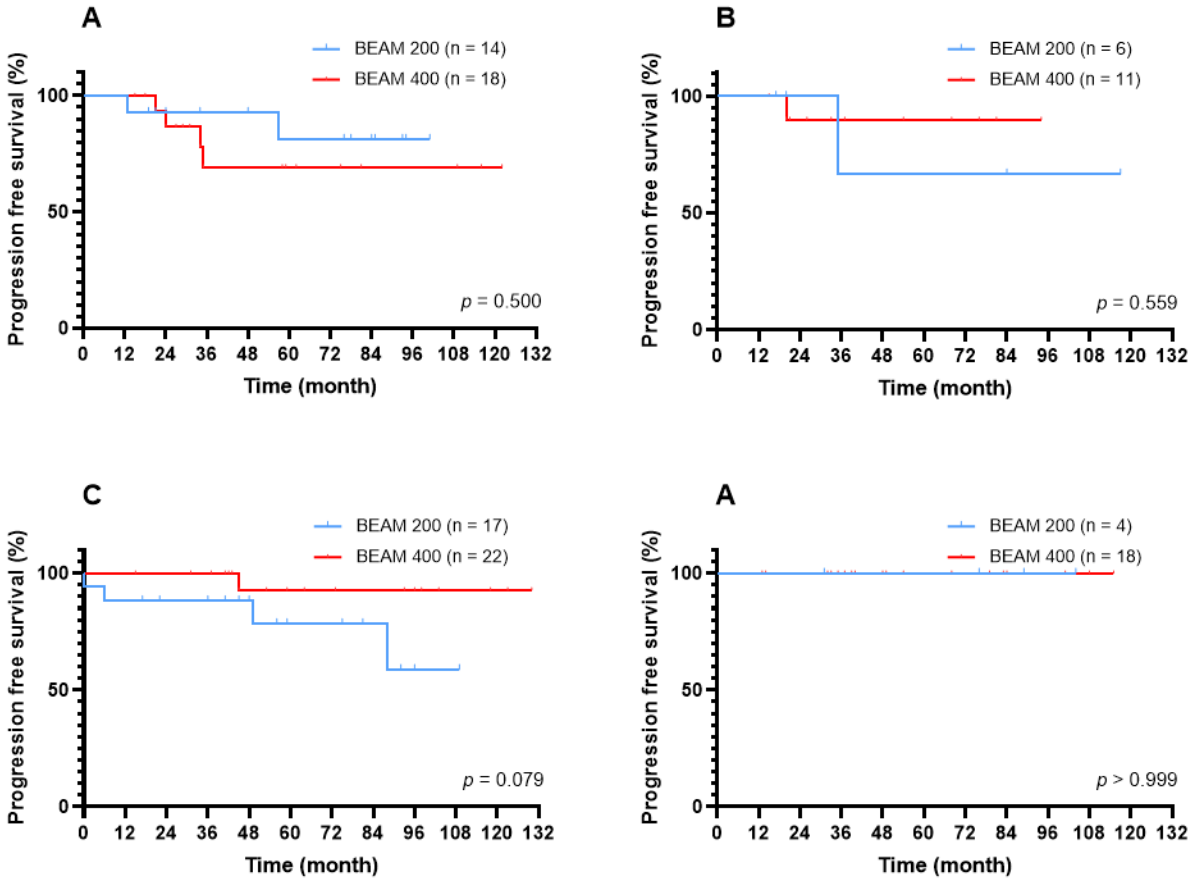
	BEAM 200	BEAM 400	*p value*
IPI score			
0	0	1	*0.438*
1	1	2	*0.886*
2	2	5	*0.622*
3	4	2	*0.125*
4	5	5	*0.382*
5	1	0	*0.192*
Undetermined	1	3	*0.605*
FLIPI score	6	11	
Low (0-1)	0	2	*0.271*
Intermediate (2)	5	5	*0.382*
High (3 ou plus)	1	4	*0.413*
Grade of FL			
1-2	4	8	*0.764*
3b	0	2	*0.271*
Undetermined	2	1	*0.285*
MIPI score	16	22	
Low risk (<5,7)	3	14	*0.068*
Intermediate (5,7-6,2)	7	4	*0.056*
High risk (6,2 et plus)	6	4	*0.119*
EORTC	1	7	
Favorable	1	3	*0.605*
Unfavorable	0	4	*0.116*
Undetermined	0	1	*0.438*
Hasenclever score	3	7	
0-2	1	4	*0.413*
≥ 3	2	3	*0.897*
Undetermined	0	3	*0.175*

Appendix III. PFS according to lymphoma histology (A) DLBCL, (B) FL, (C) MCL and (D) HL



DLBCL : Diffuse Large B Cell Lymphoma ; FL : Follicular Lymphoma ; MCL : Mantle Cell Lymphoma ; HL : Hodgkin Lymphoma

Appendix IV. OS according to lymphoma histology (A) DLBCL, (B) FL, (C) MCL and (D) HL



DLBCL : Diffuse Large B Cell Lymphoma ; FL : Follicular Lymphoma ; MCL : Mantle Cell Lymphoma ; HL : Hodgkin Lymphoma

VELY Agathe

Comparaison de la toxicité selon la posologie d'Etoposide et de Cytarabine dans le traitement des lymphomes par « BEAM »

RÉSUMÉ

Introduction : L'association de carmustine, etoposide, cytarabine et melphalan (BEAM) suivi d'une autogreffe de cellules sous périphériques est le traitement habituel des lymphomes réfractaires ou en rechute, ou dès la première ligne pour ceux présentant des facteurs de mauvais pronostic. Dans les études, l'etoposide et la cytarabine sont administrés à une dose variant de 100 à 400mg/m². Le but de cette étude est de comparer la toxicité entre deux populations : l'une recevant de la cytarabine et de l'etoposide à 400mg/m² (« BEAM 400 ») et l'autre à 200mg/m² (« BEAM 200 »).

Patients et méthodes : Cent dix patients atteints de lymphome B diffus à grandes cellules, de lymphome folliculaire, de lymphome du manteau ou de lymphome de Hodgkin et traités par BEAM étaient étudiés (41 et 69 dans les groupes BEAM 200 et 400 respectivement).

Résultats : Les patients recevaient en médiane 2 lignes de traitement avant l'intensification par BEAM. La plupart étaient en réponse complète avant traitement par BEAM (78% et 75% dans les groupes BEAM 200 et 400 respectivement). La toxicité était plus importante dans le groupe BEAM 400 avec plus de toxicité hématologique (neutropénie de 11 vs 7 jours en moyenne, p<0.001 ; aplasie fébrile de 6 vs 3 jours, p<0.001 ; 7 vs 5 transfusions en plaquettes, p=0.013) et plus de toxicité digestive (mucite présente dans 99% vs 73% des cas, p<0.001, sans augmentation des diarrhées présente dans 61% vs 54%, p=0.549). Les survies sans progression et globale étaient plus basse dans le groupe BEAM 200. Il n'existait pas de différence statistiquement significative entre les deux groupes (p=0.053 et p=0.120 respectivement), même après ajustement des facteurs confondants potentiels.

Conclusion : Le traitement par BEAM 200 permet une diminution de la toxicité hématologique et digestive, bien que la toxicité relative au traitement reste faible dans les deux groupes. Les survies sans progression et globale sont plus faibles dans le groupe BEAM 200, ces données restant statistiquement non significatives. De nouvelles études sont requises pour comparer spécifiquement ces données de survie.

Mots-clés : lymphome, autogreffe, BEAM, BEAM 200, BEAM 400, toxicité

Toxicity profile according to etoposide and cytarabine dosing in patients with lymphoma receiving autologous stem cell transplantation following BEAM conditioning

ABSTRACT

Introduction : The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by autologous stem cell transplantation (autoSCT) is a commonly used intensification regimen for relapsed/refractory or in frontline for high-risk lymphomas. Etoposide and cytarabine dosing are not well defined and varies between 100 to 400 mg.m-2 in studies with no direct comparison on tolerability and efficacy. The aim of this retrospective study was to compare toxicity and efficacy in two populations, receiving eihter 400 mg.m-2 ("BEAM 400") or 200 mg.m-2 ("BEAM 200") for both etoposide and cytarabine.

Patients and methods : One hundred and ten patients with diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma or Hodgkin lymphoma treated by BEAM regimen were enrolled (41 in the BEAM 200 group and 69 in the BEAM 400 group).

Results : Patients had received a median of 2 lines of chemotherapy prior to intensification by BEAM, most having achieved a complete response before BEAM regimen (78% and 75% in BEAM 200 and BEAM 400 groups respectively). Patients in the BEAM 400 group experienced more toxicity with more hematological (mean duration of neutropenia: 11 vs 7 days, p<0.001; duration of neutropenic fever: 6 vs 3 days, p<0.001; platelet transfusions: 7 vs 5, p=0.013) and digestive toxicity (mucositis: 99% vs 73%, p<0.001; but no more diarrhea: 61% vs 54%, p=0.549). PFS and OS were lower in BEAM 200 group, although the difference was not statistically significant between the two groups (p=0.053 and p=0.120 respectively), even after adjustment for potential confounding factors.

Conclusion : Lower etoposide and cytarabine dosing were associated with less hematological and digestive toxicities even though treatment-related toxicity remained low in both groups. PFS and OS were lower in the BEAM 200 group, but this did not reach statistical significance. Larger, multicentric, prospective studies should be carried out to define the optimal dosing.

Keywords : Lymphoma, autoSCT, autologous stem cell transplantation, BEAM, BEAM 200, BEAM 400, toxicity

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