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Impact of doxorubicin dose capping on the outcome of DLBCL patients with elevated Body Surface Area

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Letter to the editor

In 2012, the American Society of Clinical Oncology (ASCO) published guidelines regarding the dosing of chemotherapy for obese patients with cancer¹. In these patients, empiric dose reductions are often performed – usually by capping body surface area (BSA) at 2m^2 – because of concerns regarding toxicity. However, there is no evidence that administering a full dose of chemotherapy in obese patients with solid cancer is associated with an increased toxicity¹. Additionally, the ASCO guidelines highlight the negative impact on prognosis of reduced doses of chemotherapy in obese patients with solid tumors and thus recommend the use of full weight-based doses of cytotoxic chemotherapy, particularly in curable cancers¹. However, the impact of chemotherapy dosing has not been evaluated in non Hodgkin lymphoma (NHL) patients with elevated BSA.

In this study, we aimed to evaluate the impact of doxorubicin dose capping in patients with diffuse large B cell lymphoma (DLBCL). DLBCL is a curable disease in which relative dose intensity has been described to be associated with treatment efficacy². However, clinicians may be concerned with the toxicity of high doses of anthracyclins in patients with elevated BSA.

To address this question, we analysed all DLBCL patients treated in first line in one of the following prospective LYSA, GELA and/or GOELAMS trials: LNH98-5, LNH-75, LNH03-2B, and LNH03-6B^{3;4;5;6} (Supplementary Figure 1). All patients received (R-)CHOP or (R-)CHOP-like (mostly (R-)ACVBP) regimen. A theoretical BSA was calculated with Mosteller's formula for each patient according to their weight and height at inclusion. According to the dose planned in the protocol (theoretical dose) and the dose that was actually administered (observed dose), we could determine if the dose had been capped or not. Cut-off value for BSA was 2.1m^2 . Patients with a BSA of more than 2.1m^2 and doxorubicin dose capped at a BSA of 2m^2 , received less than 95% of the theoretical dose. Our cohort was divided into three groups: $\text{BSA} < 2.1\text{m}^2$ (theoretical BSA and observed $\text{BSA} < 2.1\text{m}^2$), capped $\text{BSA} \geq 2.1\text{m}^2$ (theoretical $\text{BSA} \geq 2.1\text{m}^2$ and observed $\text{BSA} < 2.1\text{m}^2$) and uncapped $\text{BSA} \geq 2.1\text{m}^2$ (theoretical BSA and observed $\text{BSA} \geq 2.1\text{m}^2$). Flow chart for patient selection is presented in Supplementary Figure 1.

A total of 1,384 patients were included in the analysis: 89% (N=1232) of the patients had a $\text{BSA} < 2.1\text{m}^2$ ($\text{BSA} < 2.1\text{m}^2$ group), 8.6% (N=119) had a $\text{BSA} \geq 2.1\text{m}^2$ and received a capped dose of doxorubicin (capped $\text{BSA} \geq 2.1\text{m}^2$ group) and 2.4% (N=33) had a $\text{BSA} \geq 2.1\text{m}^2$ and received a full weight dose of doxorubicin (uncapped $\text{BSA} \geq 2.1\text{m}^2$ group). Compared to patients with a $\text{BSA} \geq 2.1\text{m}^2$, the patients with a $\text{BSA} < 2.1\text{m}^2$ were older (74% of the patients were more than 60 years old *versus* 55.5% of patients in the capped $\text{BSA} \geq 2.1\text{m}^2$ group and 51.5% of patients in the uncapped $\text{BSA} \geq 2.1\text{m}^2$ group, $p < 0.001$), had a lower BMI (58.8% had a $\text{BMI} < 25\text{kg/m}^2$ *versus* 3.4% and 9.1%, respectively, $p < 0.001$), were predominantly females (49.3% *versus* 10.1% and 6.1%, $p < 0.001$), had a higher aalPI score (47% had an aalPI score > 1 *versus* 37.8% and 30.3%, $p < 0.001$) and had more B symptoms (36.2% *versus* 20.2% and 18.2%, $p < 0.001$) (Supplementary Table 1). Groups were comparable for the following factors: Ann Arbor stage, number of extra nodal lesions and treatment regimens (R-CHOP, CHOP and R-ACVBP).

The rate of treatment-related death was 3.9% in the $\text{BSA} < 2.1\text{m}^2$ group, 6.7% in the capped $\text{BSA} \geq 2.1\text{m}^2$ group and 6.1% in the uncapped $\text{BSA} \geq 2.1\text{m}^2$ group. These differences were not statistically significant ($p = 0.293$) (Table 1).

PFS and OS for the three groups are shown in Figure 1. Median PFS was 78.7, 75.9 and 57.9 months for patients with $\text{BSA} < 2.1\text{m}^2$, capped $\text{BSA} \geq 2.1\text{m}^2$ and uncapped $\text{BSA} \geq 2.1\text{m}^2$, respectively. Median OS was 106.5, 113.1 and 93.1 months, respectively. There was no statistical difference between the groups for PFS nor OS ($p = 0.481$ and 0.864 ,

respectively)(Table 1). These results remained unchanged after adjusting for sex, aalPI score and BMI (Supplementary Table 2).

Our study did not show any impact of doxorubicin dose capping at 2m^2 on PFS nor OS in DLBCL patients with elevated BSA. Similar results were reported by Kempf *et al* in AML patients with an elevated BSA, except for the subgroup of obese patients with a favourable cytogenetic risk⁷. Changes in the pharmacokinetics of doxorubicin in patients with elevated BSA may have neutralized the impact of dose capping on the outcome. Indeed, doxorubicin clearance is reduced in obese patients thereby increases doxorubicin exposure^{8,9}. In NHL patients, some retrospective studies have found that the outcome was better^{10,11} or similar¹² in overweight and obese patients receiving full weight chemotherapy dosing compared to patients with normal BMI. Such difference was not found in the current study.

The treatment-related mortality did not differ between the three groups although high BMI and cumulative dose of anthracycline have been associated with higher risk of anthracycline cardiotoxicity¹³. In our study, the influence of confounding factors such as age, sex, performance status, and comorbidities could not be excluded. Ganti *et al* reported a lower incidence of treatment-related mortality in obese NHL patients, and a trend in overweight patients¹⁴. Other studies reported similar rates of hematologic and non-hematologic toxicities in full-dosed overweight and obese patients compared with normal weight patients^{9,10,12}.

Interpretation of these results requires caution because of some limitations. First, this is an unplanned retrospective analysis. Second, the sample size of the patients with an elevated BSA and an uncapped dose of doxorubicin is small and may have underpowered the capacity to detect any statistical difference in survival or treatment-related mortality. Indeed, the power estimated for the PFS analysis with this sample size was 60%. Finally, the groups were not comparable for several prognostic factors that may influence prognosis and toxicity.

In conclusion, our study did not demonstrate inferior efficacy when doxorubicin dose was capped at 2m^2 in DLBCL patients with elevated BSA. On the other hand, uncapped dosing of doxorubicin did not seem to increase the incidence of treatment-related mortality. Therefore, these two options seem acceptable in DLBCL patients with elevated BSA.

Contribution: R.H. and M-A. L. designed the research, analyzed data and wrote the paper. C.G. and S.B. analyzed data and wrote the paper. R.D., N.M., L.O., B.C., C.H., H.T., G.S., and T.L. provided the data and wrote the paper. All authors reviewed and approved the final draft.

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Figure 1. Progression-free survival (A) and overall survival (B) according to BSA and doxorubicin dose adaptation in patients with DLBCL (Log-rank p=0.481 and p=0.864, respectively).

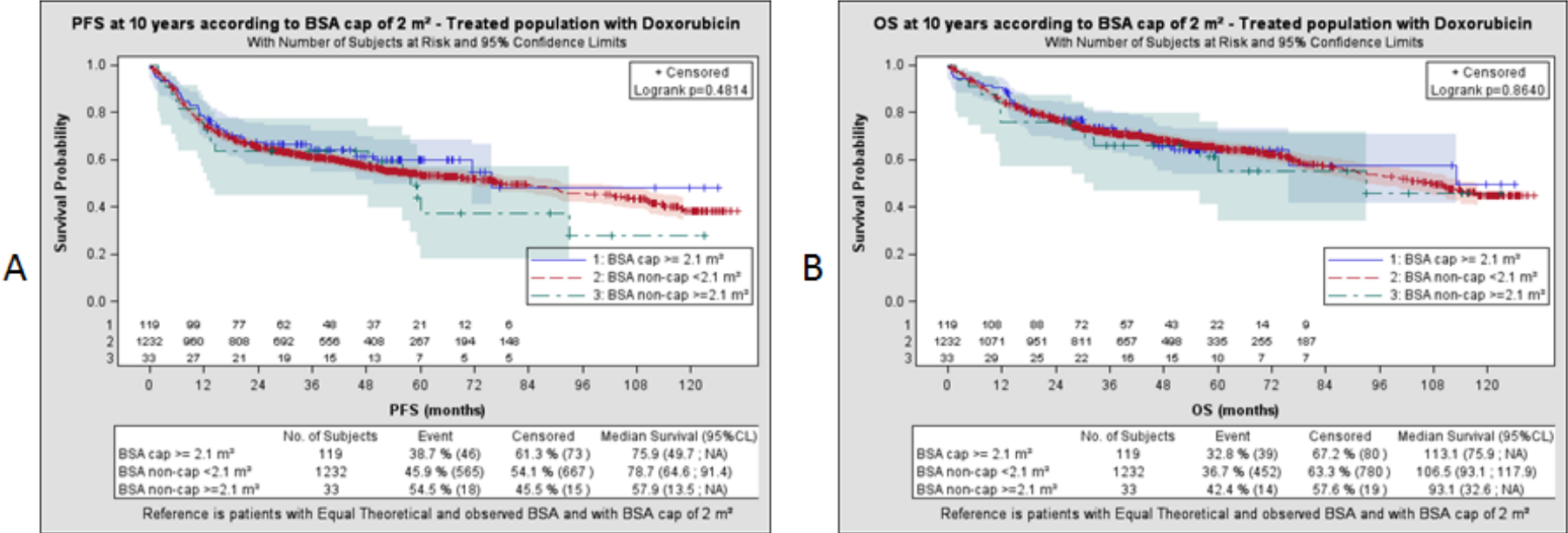


Table 1. Treatment-related mortality, progression free survival and overall survival according to BSA and doxorubicin dose adaptation in patients with DLBCL.

	BSA<2.1m²	BSA capped≥2.1m²	BSA uncapped≥2.1m²	p value
Number (%)	1.232 (89%)	119 (8.6%)	33 (2.4%)	
Treatment-related mortality	3.9%	6.7%	6.1%	0.293 ¹
Median PFS (95%CI)	78.7 [64.6 ; 91.4]	75.9 [49.7 ; NA]	57.9 [13.5 ; NA]	0.481 ²
Median OS (95%CI)	106.5 [93.1 ; 117.9]	113.1 [75.9 ; NA]	93.1 [32.6 ; NA]	0.864 ²

¹ χ^2 test was performed.

² Log-rank test was performed. Test was two sided.
Significance level is p<0.05

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