Baseline metabolic tumor burden in DLBCL affects response to immuno-chemotherapy and patients outcome through influence of rituximab pharmacokinetics. A LYSA group study

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OBJECTIVES

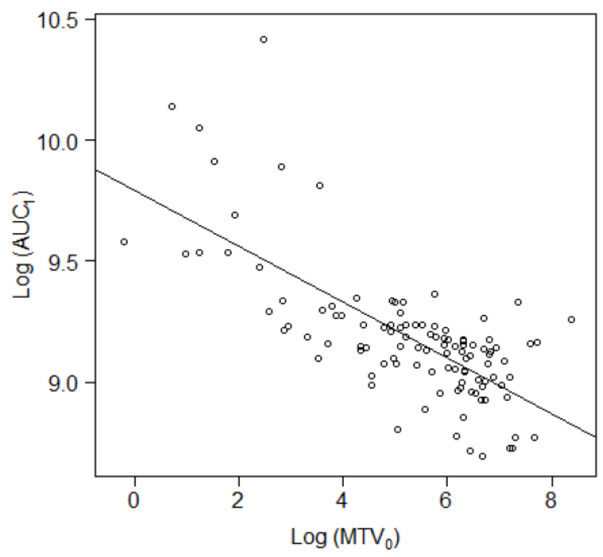
Immuno-chemotherapy associating rituximab (MabThera®, Rituxan®) and anthracycline based chemotherapy (*ie* CHOP or ACVBP) has dramatically improved survival of pts with DLBCL. However, some pts failed to respond or relapsed early after treatment with poor prognosis. Among factors affecting response to treatment, murine model has suggested that tumor burden could affect rituximab exposure and efficacy. To evaluate the role of tumor burden on response to immuno-chemotherapy, we have analyzed the metabolic baseline tumor volume (MTV_0) using PET and rituximab pharmacokinetics (PK) in a cohort of pts receiving immuno-chemotherapy.

METHODS

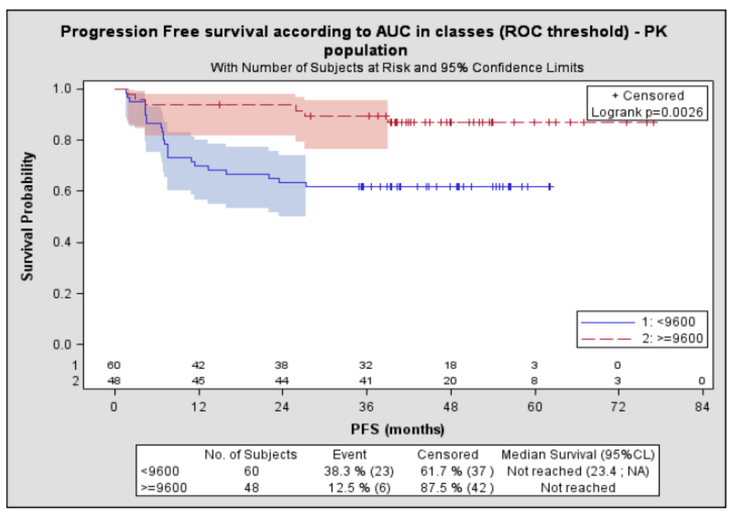
- 108 ps with DLBCL from two prospective multicenter studies were evaluated for metabolic tumor volume and rituximab PK. Pts with localized stage (n=19) were included in GOELAMS 0203 trial (NCT00841945) whereas advanced stage (n= 89) were included in GELA 073B trial (NCT00498043).
- All patients received rituximab (375 mg/m^2) associated with anthracycline based chemotherapy administered every 14 days (CHOP14 or R-ACVBP).
- Rituximab concentrations were measured before and after each rituximab infusion, on day 5 of each cycle, and 2 to 3 weeks after the fourth cycle.
- Baseline metabolic tumor volume (MTV_0) was evaluated by PET as previously published *(Meignan M et al, EJNM 2014;41:1113)*.
- Rituximab PK was assessed using compartmental modelling and the influence of MTV_0 was tested as a covariate on PK parameters.
- Logistic regression was applied to evaluate the influence of MTV_0, on rituximab exposure (AUC), metabolic response (after C4, according to international criteria) and patients' outcome (PFS and OS).
- AUC values were dichotomized using ROC curve and the PFS and OS of patients above or below the cutoff were compared using a logrank test.

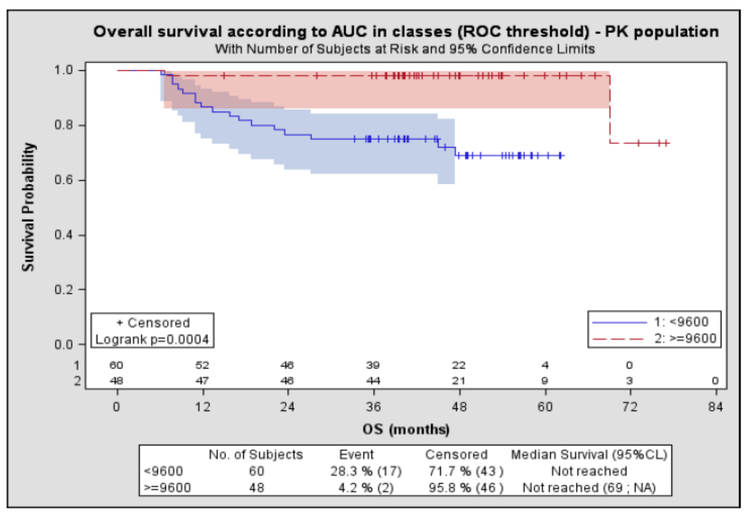
RESULTS

- At baseline assessment, median MTV_0 was 313.5 cm^3 (range 0.8 - 4339 cm^3)
- Lower rituximab AUC1 was observed for high MTV0 (R^2 = 0.51, p < 0.0001)



- After four cycles of R-Chemo, ORR was 91.7% including 39.3% of CR.
- The cutoff of AUC1 allowing with the best sensitivity and specificity to discriminate responder patients and patients with different outcome was 9600 mg.h/L.
- With a median follow up of 48 months, patients with an AUC1 ≥ 9600 mg.h/l (n=48, 44%) had a significantly better 4y-PFS (87% vs 62%; HR= 0.276, P=0.0026) and 4y-OS (98% vs 69%; HR, P =0.0004) than those with an AUC1 under the cutoff.





CONCLUSIONS

The baseline metabolic tumor volume impacts significantly the outcome of DLBCL patients treated by immuno-chemotherapy (ICML 2015, Abstract 083). Our results suggest that MTV_0 affects patients outcome through its influence on rituximab PK and encourage to develop MTV_0 adapted rituximab dosing.

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