FEASIBILITYAND EFFICACY OF POST-TRANSPLANT CONSOLIDATION IMMUNOTHERAPY WITH NIVOLUMAB SUPPORTED BY THE REINFUSION OF UNSELECTED AUTOLOGOUS LYMPHOCYTES IN PATIENTS AFFECTED BY RELAPSED/REFRACTORY HODGKIN LYMPHOMA

KEYWORDS: Hodgkin Lymphoma, Autologous stem cell transplantation, Nivolumab

BACKROUND

Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin with an high probability of long-term survival.Despite high efficacy of frontline therapy, about 30% of patient will show relapse or refractory disease (R/R). In this patient population, the treatment of choice consists of salvage chemotherapy followed by intensive conditioning regimen and autologous stem cell transplantation (ASCT). However 30-50% of patient receiving salvage chemotherapy fail to achieve at least PR and further therapy with Brentuximab-Vedotin (BV) may be administered to induce a clinical response. BV may be further used as post-ASCT consolidation therapy, especially in patient who receive ASCT in PR. However therapeutic options for truly refractory patients are still limited.

Recently, the efficacy of immune-check point inhibitors have been explored in HL and the PD-1 targeting antibody Nivolumab, has shown promising results in HL patients relapsed after ASCT. Nivolumab is currently approved with this indication. Unfortunately, expected CR rate is only about 20%. Thus, we reasoned that earlier administration of nivolumab, as post-ASCT consolidation, may improve its efficacy. However, several reports have highlighted the importance of patient immune-competence, which is severely impaired in heavily pre-treated lymphoma patients undergoing ASCT, to achieve durable response with anti-PD1 immunotherapy. In this view, there is a strong rationale for reinfusing autologous lymphocytes, early after ASCT, concomitant with anti-PD1 consolidation immunotherapy in very high risk HD patients.

AIMS OF THE STUDY

Here we report the preliminary results of a prospective trial investigating the feasibility, and the efficacy, in terms of both immunological recovery and clinical response, of post-ASCT Nivolumab with the support of unselected autologous lymphocyte reinfusions (ALI).

METHODS

Patients under the age of 60 with high risk HD identified by PET2 or PET6 positivity following ABVD, were scheduled for a pre-emptive lymphocyte apheresis, with a target of $5x10^7$ CD3+/kg. Patients who failed to achieve at least PR with salvage chemotherapy proceeded to ASCT with FEAM conditioning followed by early Nivolumab and ALI. The first ALI was performed 7 days after engraftment; the second ALI was administered at day +14 after the first dose whereas the third and the fourth doses were given every 21 days. ALI dosing was incremental, one logarithm at each infusion,

starting from $1x10^4$T cells/kg in the first infusion to a maximum of $1x10^7$/kg in the fourth and last infusion. Each ALI was followed within 48 hours by the administration of Nivolumab 240 mg flat dose.

Toxicity was evaluated and graduated according to CTCAE-EORTC standards. Circulating Lymphocyte subpopulations were extensively studied before and after each ALI and each Nivolumab administration by 12-colours flow cytometry. Clinical response was evaluated 21 days after completion of the fourth ALI + Nivolumab.

PRELIMINARY RESULTS

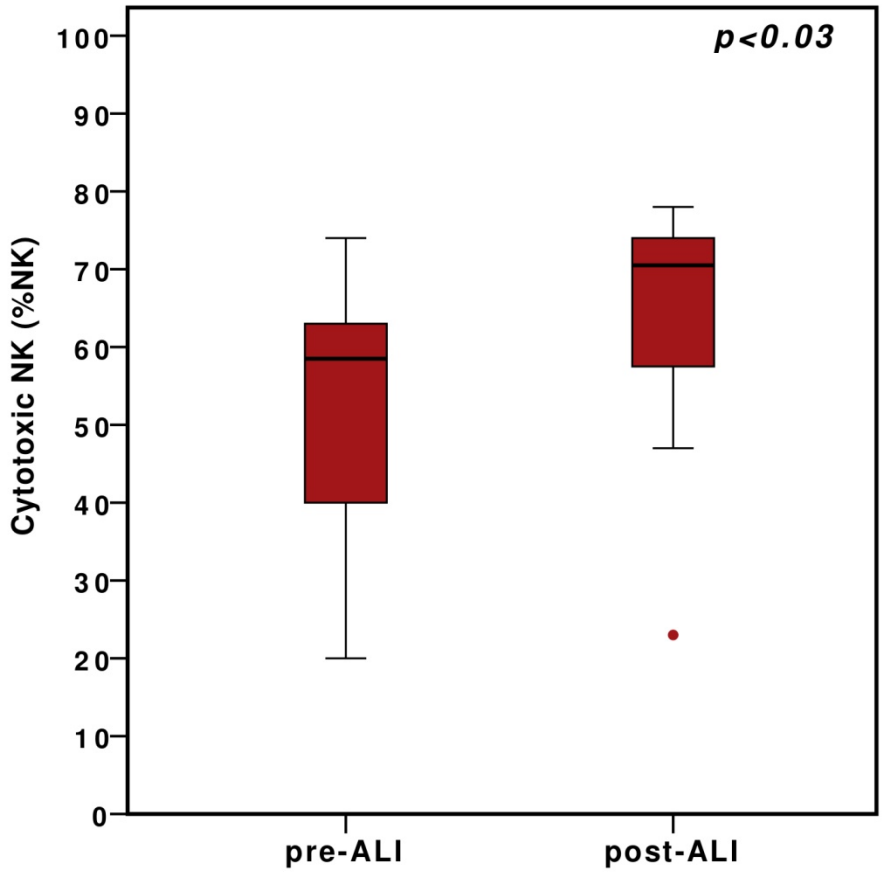
FourR/R HD patient have completed the treatment and 3are currently under treatment. All patient failed to achieve CR with first and second line chemotherapy and then progressed during BV therapy. PET scan before ASCT showed progressing disease in all patient, with multiple-extra nodal involvement in 3 of them. All patient underwent ASCT with FEAM conditioning and achieved complete engraftment after a median of 10 days (8-12).

Compared to HD patients receiving the same conditioning without ALI, in all patients a quicker immune-recovery in term of CD3+ count was achieved at all timepoints ($p < 0.05$). After ALI administration, cytotoxic (CD56+,CD16+,CD57+) NKcells showed the most significant consistent increase (Fig. 1, $p<0.05$). Nivolumab administration by itself determined only a modest and transient increase in T-effector population. No grade 3 or 4 adverse events were recorded so far. In one patient grade 2 fever was observed after 1st ALI. All treated patient achieved negative PET scan after the procedure and are alive and disease-free after a median follow-up of 9 months.

PRELIMINARY CONCLUSIONS

Post-ASCT ALI proved to be feasible and effectiveallowing a faster immune recovery in heavily-pre-treated HD patients.Moreover, the early administration of check point inhibitors combined with ALI as post-ASCT consolidation therapy, may improve the low rate of CR expected with anti-PD1 blockade alone, providing a more effective option for refractory patient, which are usually considered not candidate for ASCT.

Fig.1: Cytotoxic NK cell/ul before and after ALI.



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