# CLINICAL EXPERIENCE WITH PROTON RT IN PATIENTS WITH REFRACTORY OR RELAPSED B-CELL HEMATOLOGIC MALIGNANCIES TREATED WITH CAR T-CELL THERAPY

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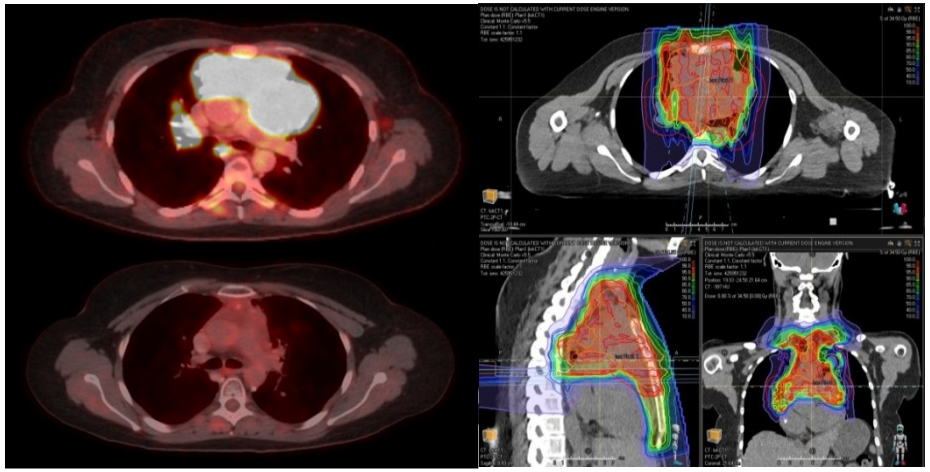

Pt13, 31yo woman M.V., dg. 11/2023, R/R B-NHL, PMBL, progressed on 2 lines of initial treatment, bridge proton RT PBS in DIBH, 34.5 CGE/15fx + boost 10CGE/5fx, combination with nivolumab and brentuximab vedotin, Left: upper- before RT, lower-3 months after RT achieved CR, Right: treatment plan

## Background and aims:

Refractory or relapsed highly aggressive B-cell lymphoma (R/R HGBL) or B-cell acute lymphoblastic leukaemia (R/R B-ALL) are clinical situations associated with an unfavourable prognosis. A new promising approach is immunotherapy using chimeric antigen receptor T-lymphocytes (CAR-T). However, only 40-50% of pts treated with CAR-T achieve a long-term response. Radiotherapy (RT) appears to be an appropriate modality to improve outcomes. RT causes cytoreduction and can also stimulate the immune response at different levels. Proton RT is not only associated with the possibility of a safer RT with curative dose[1], but may also be associated with a lower risk of RT-related immunosuppression due to a lower risk of radiation-induced lymphopenia (RIL).

## Conclusions:

Comprehensive bridging RT to CAR-T treatment is likely associated with better PFS and OS[2]. The inclusion of proton RT in bulky progressive lymphoma infiltrates in unfavourable locations (mediastinum) or multiple foci in different locations seems very promising. In our experience, proton RT with curative dose is associated with acceptable toxicity. Thus, proton RT can safely extend the therapeutic options of RT. Our limited patient cohort shows a trend toward better treatment outcomes when RT is included as a bridge to CAR-T instead of salvage therapy after CAR-T failure. In our cohort indicated for bridging RT, RT enabled the application of CAR-T therapy in all patients.

| Pt ID | Age at RT [years] | Sex | Diagnosis | Stage | Time to end of RT after diagnosis [months] | Time to CAR-T after diagnosis [months] | RT region | Bulk size in time of RT ≥ 10 cm Yes/No | Number of cycles systemic treatments before RT | CAR-T bridge Yes/No | Treatment dose [CGE] | Radical RT Yes/No | CAR-T type | Acute RT toxicity | Late RT toxicity | CAR-T CRS toxicity | CAR-T ICANS toxicity | Post CAR-T+RT salvage therapy Yes/No | Post RT progression in-field/out-of-field/both | Current state | Time to progression after diagnosis [months] | Type of salvage treatment after RT | follow-up [months] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt1 | 45 | M | follicular B-NHL | IV | 43 | 30 | L parotid gland + L neck | Y | 6 | N | 30CGE/15fx | Y | Clinical study CART-T | skin gr.I, dysphagia gr.I | N | N/A | N/A | N | N | CR | | | 23 |
| Pt2 | 66 | F | DLBCL | IV | 9 | 12 | T10 vertebra+L pelvis | N | 2 | Y | 40CGE/20fx | Y | Kymriah | 0 | 0 | N/A | N/A | Y | in field | CR | 9 | 3xpola + BR | 35 |
| Pt3 | 49 | M | DLBCL | IV | 16 | 13 | craniospinal axis+boost | N | 4 | N | 24CGE/12fx +6 CGE/3fx | Y | Kymriah | 0 | N/A | N/A | N/A | N | out of | † in PD | | | 3 |
| Pt4 | 51 | M | DLBCL | IV | 12 | 10 | infiltration of colon | Y | 3 | N | 40CGE/20fx | Y | Kymriah | GIT gr.I | N/A | N/A | N/A | N | out of | † in PD | 3 | | 17 |
| Pt5 | 28 | F | pre-B-ALL | N/A | 52 | 53 | craniospinal axis | N | 5 | N | 18CGE/9fx | Y | Tacartus | neurologic gr.I | neurologic gr.I | N/A | N/A | Y | both | † in PD | 16 | reRT C+LS spinal roots, L neck 23CGE/10fx | 19 |
| Pt6 | 48 | M | DLBCL | IV | 79 | 82 | craniospinal axis+boost | N | 2 | Y | 20CGE/10fx +boost 10 CGE/5fx | Y | Yescarta | neurologic gr.I | neurologic gr.I | CRS I | ICANS IV | Y | out of | CR | 16 | 2xobinutuzumab, 6xglofitamab | 24 |
| Pt7 | 45 | M | DLBCL | IV | 19 | 21 | mediastinum+ L hilus | N | 2 | Y | 39CGE/13fx | Y | Yescarta | dysphagia gr.II | pneumonitis gr.I | CRS III | ICANS III | N | N | CR | | | 25 |
| Pt8 | 67 | F | DLBCL | IV | 20 | 21 | L breast+mediast. +retroperit. | Y | 3 | Y | 22CGE/10 fx+24CGE/12fx (mediast.+RP) | N | Kymriah | dysphagia gr.III | 0 | N/A | N/A | Y | out of | CR | 6 | 12x glofitamab | 20 |
| Pt9 | 71 | M | mantle B-NHL | IV | 106 | 107 | paravertebral infiltrate ( L1-L4) | Y | 3 | Y | 39CGE/13fx | Y | Brexucel | skin gr.I | fibrosis gr.I | CRS III | 0 | N | N | CR | | | 15 |
| Pt10 | 29 | M | DLBCL | IV | 11 | 10 | R neck | N | 3 | N | 39CGE/13fx | Y | Yescarta | mucositis gr.II, skin gr.I | 0 | CRS I | ICANS III | Y | N | CR | | | 18 |
| Pt11 | 31 | M | DLBCL | II | 13 | 5 | R neck + R tibia | N | 3 | N | 39CGE/13fx (neck), 20CGE/5fx(tibia) | Y | Yescarta | dysphagia gr.I, skin gr.I | 0 | N/A | N/A | Y | out of | PD | 0 | RT mediast. 41.4CGE/18fx, 3xpola + BR 3 cycles, 3xglofitamab | 13 |
| Pt12 | 57 | M | DLBCL | II | 11 | 7 | mediastinum | Y | 3 | N | 50CGE/25fx | Y | N/A | dysphagia gr.II, skin gr.I | N/A | CRS II | 0 | Y | both | † in PD | 3 | reRT mediastinum 20CGE/5fx | 7 |
| Pt13 | 31 | F | PMBL | IV | 5 | 7 | mediastinum | Y | 2 | Y | 34.5 CGE/15fx + boost 10CGE/5fx | Y | Yescarta | dysphagia gr.I, skin gr.I | 0 | CRS I | ICANS III | N | N | CR | | | 10 |
| Pt14 | 46 | M | PMBL | I | 8 | 9 | mediastinum | Y | 1 | Y | 34.5 CGE/15fx + boost 10CGE/5fx | Y | Yescarta | skin gr.II | 0 | 0 | 0 | N | N | CR | | | 8 |
| Pt15 | 42 | M | DLBCL | IV | 6 | 8 | mediastinum | Y | 2 | Y | 4CGE/1fx + 27.6CGE/12fx | Y | Yescarta | dysphagia gr.II | pneumonitis gr.I | CRS I | 0 | N | N | CR | | | 5 |

## Idea to share

In our experience, we prefer to use bridging RT over salvage RT. We find the idea of performing lymphocyte apheresis in the first week of RT interesting. At this time point, some lymphocytes might already be naturally stimulated against the tumour due to the breakdown of some tumour cells by RT.

1. Saifi O, Kharfan-Dabaja MA, Zeidan YH, et al.. Proton Therapy as a Bridging Treatment in CAR T-Cell Therapy for Relapsed and Refractory Large B-Cell Lymphoma: Is There a Role? Int J Part Ther. 2020 Jun 3;7(1):13-20. doi: 10.14338/IJPT-20-00004.1. PMID: 33094131; PMCID: PMC7574825.
2.Yegya-Raman N, Plastaras JP, Wright CM,et al. Bridging Radiotherapy Prior to Chimeric Antigen Receptor T-Cells for B-Cell Lymphomas: An ILROG Multicenter Study. Blood Adv. 2025 Apr 9:bloodadvances.2025015855. doi: 10.1182/bloodadvances.2025015855. Epub ahead of print. PMID: 40203192.