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GERMINAL CENTER B-CELL DIFFUSE LARGE LYMPHOMA DOUBLE HIT REFRACTORY TO CHEMOIMMUNOTHERAPY: A CASE REPORT

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL). Double-hit lymphoma is a colloquial term for high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Lymphoma with DLBCL morphology may be subclassified into germinal center B cell (GCB) DLBCL and activated B cell (ABC) DLBCL. The gold standard treatment includes R-CHOP. R-CHOP cures approximately 60% of patients with DLBCL; however, 30-40% relapse and 10% are refractory to treatment. Approximately 50% of patients with relapsed or refractory DLBCL respond to second-line chemotherapy; however, they have a poor prognosis.

CASE REPORT

A 58-year-old male diagnosed with GBC DLBCL subtype with *c-MYC* and *BCL2* rearrangements (Ann Arbor IV-b stage) (Fig. 1a) was initially treated with two cycles of R-CHOP and achieved a dissociated metabolic response, according to PET (Fig. 1b). A second line of treatment included two cycles of R-EPOCH. After three cycles, PET showed metabolic progression. We escalated treatment to 2 cycles to R-ESHAP. PET and clinical evaluation showed a partial metabolic response with the persistence of lymphoproliferative disease.

CAR-T (chimeric antigen receptor T) cell therapy was initiated (Fig. 2). After CAR-T therapy, PET showed a good partial response (Deauville score (DS) 4) (Table 1). Two months later, a right infraclavicular subcutaneous mass indicated progression of the GCB DLBCL (DS 5) (Fig. 1c). The patient was enrolled in a clinical trial comparing brentuximab, vedotin, or placebo in combination with lenalidomide and rituximab (ECHELON-3). After two cycles, the pectoral mass increased as accompanied by the appearance of 2 adjacent lesions (Fig. 3). A new PET showed GCB DLBCL criteria with DS 5.

The patient was included in a double-blind trial as a fifth line of treatment. He received R-Pola-Benda. After two cycles, PET showed progressive disease . The patient was included in a new phase 1 clinical trial (CD20/CD47). After two cycles, examining the patient showed evidence of progression (DS5). Currently, the patient is waiting for a seventh line of treatment with Epcoritamab.

DISCUSSION

Non-Hodgkin lymphoma (NHL) comprises a diverse group of malignant tumors of lymphoid tissues variously derived from the clonal expansion of B cells, T cells, natural killer cells, or lymphoid precursors. The pathogenesis of lymphomas involves accumulation of multiple genetic lesions affecting proto-oncogenes and tumor suppressor genes. A cell of origin has been proposed for each type of NHL based on morphologic, immunophenotypic, and genetic features of the malignant cells, but many cases are not clear cut. The vast majority are derived from germinal center or post-germinal center B cells. Major genetic modifications occur during the normal germinal center reaction of B cells. These changes (class-switch recombination and somatic hypermutation) are required for normal immune development, but also place the cell at risk of acquiring additional mutations that may be oncogenic. The molecular pathogenesis of DLBCL is complex and includes both genetic lesions that are relatively specific for this disease (ie. rearrangements of BCL6) and molecular alterations that are shared with other NHL variants. MYC translocation is found in 5-15% of GBC DLBCL.

DLBCL is curable in approximately half of cases with current therapy, particularly in those who achieve a complete remission with first-line treatment. When MYC translocation appears alone. Its effect on survival in treated patients with R-CHOP it has been discordant in studies. This discrepancy is explained because adverse effects seems to occur only with the partner of the MYC translocation is the gene IgH8.90. There are also discrepancies on the prognosis of the translocation of isolated BLc2 or BCL691-93, although the translocation of BLC2 seems to have an adverse role in these lymphomas. MYC translocation is frequently associated with that of BCL2 and, less frequently, with that of BCL6, resulting in double or triple hit lymphoma, which constitutes the new entity in the classification of WHO of “High grade B lymphoma with rearrangement of MYC and BCL2 and/or BCL6”, that do seem to have a clearly worse prognosis.

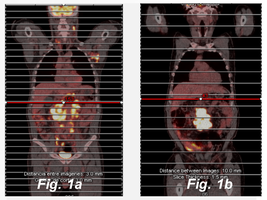


Figure 1: a) PET at the moment of diagnosis; b) PET showed dissociated metabolic response; c) PET showed progressive disease.

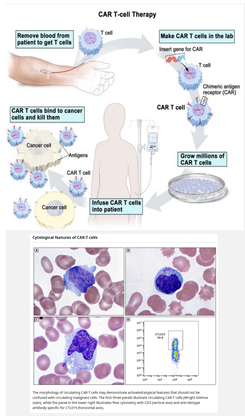


Figure 2: CART-T (chimeric antigen receptor T) cell therapy scheme.

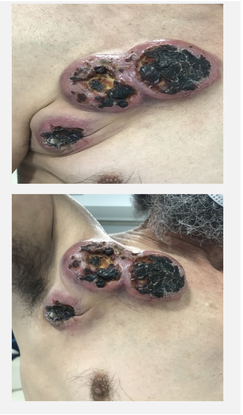


Figure 3: Right infraclavicular subcutaneous mass indicated progression of the GCB DLBCL.

Table 1: The Deauville score for interpreting FDG-PET in lymphoma.

Score	Findings
1	No uptake
2	Uptake ≤ mediastinal blood pool
3	Uptake > mediastinal blood pool but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Uptake markedly higher than liver (i.e. 2 to 3 times the maximum SUV in the liver) and/or new lesions
X	New areas of uptake unlike to be related to lymphoma

The Deauville score (also known as the 5-points scale) is a purely visual method of standardizing the interpretation of post-treatment PET scans for primary nodal lymphoma allowing for the comparison of scan performed using different machines at different centers. The Deauville score uses a patient’s FDG uptake in the mediastinal blood pool and liver as an internal control. FDG uptake is always present in these 2 sites, with higher levels consistently seen in the liver. The Deauville score interprets FDG avidity of suspected disease (most intense uptake in a site of initial disease) in relation to FDG uptake in these 2 locations.

NOTE: If mediastinal blood pool activity is equal to or greater than activity in the liver, then the uptake within the lesion should be compared with that in the liver (uptake lesion < liver score 2; lesion = liver score 3).

FDG: fludeoxyglucose; PET: positron emission tomography; SUV: standardized uptake value.

CONCLUSION

Treatment of advanced-stage DLBCL with curative intent using rituximab-based chemotherapy is associated with long-term survival in more than two-thirds of patients. We described a case of double hit GBC DLBCL refractory to chemoimmunotherapy and CAR-T therapy.

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