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Case Report
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Overcome after Special Use of Bridging Therapy in Refractory DLBCL Subsequently Treated with CAR-T Cell

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Abstract

Our case report is about a 63-year-old patient diagnosed with a refractory highly biologically aggressive cervical diffuse large B-cell lymphoma as malignant transformation from gastric follicular lymphoma. Meanwhile she was presented as a candidate for CAR-T treatment, due to clinical risk of airway obstruction by the tumor, she underwent an intensive bridge therapy based on radiotherapy concomitant with chemotherapy and targeted therapy in our center. As far as we know, these combinations of treatments have never been used before. Our objective is to show the good results in terms of response and survival in our patient after CAR-T cell infusion.

Introduction

Follicular Lymphoma (FL) was the first neoplasm of our patient. FL makes up 35% of Non-Hodgkin Lymphomas (NHLs) [1]. It is an indolent lymphoma with a good response to chemoimmunotherapy and radiotherapy; however in 3% of cases, it undergoes a malignant transformation to Diffuse Large B-Cell Lymphoma (DLBCL) [2]. They can be cured by the first line of treatment, but up to 40% of them will relapse in the following years, more frequently in the first two years [3]. It confers a very poor prognosis since it is resistant to salvage chemoimmunotherapy, as unfortunately, in the case of our patient.

Outside of a clinical trial, Chimeric Antigen Receptor (CAR)-T cell therapy is currently the best therapeutic option for those patients since results of ZUMA-1 [4] and JULIET [5] trials where published. CAR-T cells are a form of genetically-modified immunotherapy that uses the patient's own T lymphocytes (i.e. autologous T cells). CAR-T cells are transfected with a gene that encodes a CAR to direct the patient's T cells against the lymphoma cells. This process is performed *ex vivo*, expanded in a production facility, and then infused back into the patient as therapy.

Sometimes administration of bridging therapy for reducing tumor burden or palliation of lymphoma symptoms while awaiting CAR-T infusion is required. In his case report we show the results of our patient's clinical outcome after CAR-T cell treatment using involve site radiotherapy concomitant plus chemotherapy and targeted therapy as part of bridge therapy.

Material and Methods

We present a Caucasian 63-year-old women diagnosed with gastric FL in 2010. She presented a bulky gastric mass and para-aortic and retroperitoneal adenopathies. It is classified as Ann-Arbor Stage IV by bone marrow infiltration. The primary treatment consisted in 8 cycles of R-CHOP every 21 days and consolidation with radiation therapy on the residual gastric mass, in April 2011. She achieved a complete response in PET and bone narrow. She continued maintenance rituximab for two years until 2013.

Six years later, she had her first nodal relapse located on right side of the neck (Figure 1). The biopsy indicated a transformation of follicular lymphoma into DLBCL Centro germinal immunophenotype. PET/CT scan showed uptake of the right supraclavicular and hilar lymph nodes. She was eligible for an autologous Hematopoietic Cell Transplantation (HCT) so salvage chemoimmunotherapy with 3 cycles of R-ESHAP every 21 days was given. She achieved complete functional response by PET/CT in May 2019.

In the following month she had an early local relapse. R-MINE was used as rescue scheme for the patient but given the refractory disease by the growth of lymphoma in cervical nodes, she was

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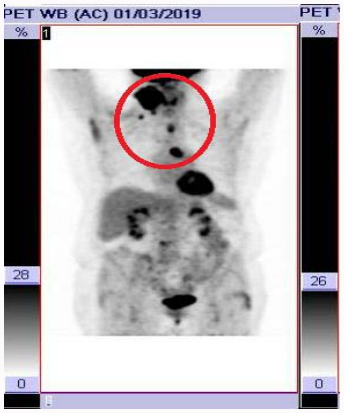

Figure 1: Relapse of transformed follicular lymphoma.

considered as a candidate for CAR-T cell therapy. Meanwhile, we started a third line chemotherapy with R-GEMOX. Good clinical response was observed for the first week, but at the second one the tumor presented an aggressive biological growing and high risk of airway obstruction. The patient referred dysphagia, pain, cough and facial deformity.

Once the apheresis of lymphocytes for the preparation of CAR-T cell was performed, we decided to use Polatuzumab + Bendamustine + Rituximab as intensive bridge therapy in concomitance with involved site Radiotherapy total dose of 40 Gy, 2 Gy per fraction (Figure 2). A complete clinical response was obtained within a week after the end of the treatment. Tolerance to the combination was moderate, requiring hospitalization due to febrile pancytopenia with grade-2 mucositis and dysphagia. The patient recovered from the clinical and hematological toxicity in the following month.

Finally CAR T cells therapy (tisagenlecleucel) were infused in December 2019. The patient achieved a complete metabolic and clinical response maintained for 12 months after this (Figure 3). Nowadays, the patient is reviewed in our departments for plaquethopenia as cronical secondary effect after CAR-T cell therapy. The patient leads a normal life, working hard in the field.

Results and Discussion

Refractory primary disease or relapse of DLBCL who cannot be rescued by bone marrow transplantation confers a very poor prognosis [6,7]. Axicabtagene ciloleucel and tisagenlecleucel are anti-CD19 CAR-T-cell therapies has been FDA-approved as the main treatment for this patients after 2 or more prior systemic therapy regimens. According to the results of the multicenter phase II study JULIET trial (5) they reach an Overall Survival (OS) rate at 12 months of 49% for all patients and 90% for those with a CR.

As it is shown in a retrospective study from University of Pennsylvania [8], bridging therapy is required in a 69% of cases. Therapies most commonly received were combination chemoimmunotherapy (21%), obinutuzumab (15%), ibrutinib (15%), only radiotherapy (15%), systemic therapy + radiation therapy (12%), lenalidomide (6%), cyclophosphamide (3%), and rituximab/lenalidomide (3%).

74% of relapses and progressions in refractory cases are located in the original site [9]. And as it is shown in retrospective series, radiotherapy improves local control and reduces relapse rate in patients (36% *vs.* 55%) [10]. Therefore, there is strong rationale to use

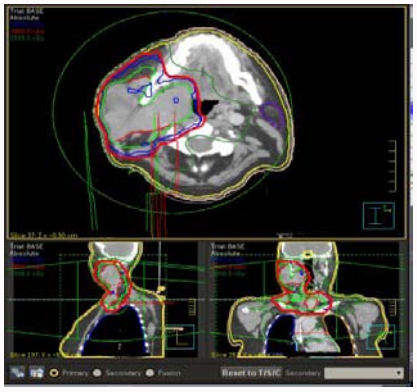

Figure 2: Radiation Planning Treatment.

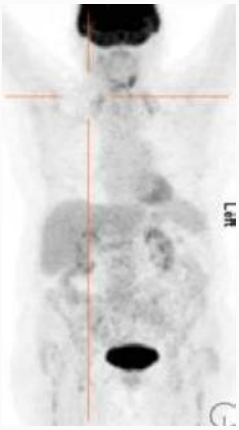

Figure 3: Complete response.

a Radiotherapy (RT) bridge during the cell manufacturing process for palliation, local control and cytoreduction.

In a study from MSKCC [11], 13 patients were treated with RT after CAR T cell apheresis (the most common RT regimen was 20 Gy in 5 fractions, range 20 Gy to 47 Gy) suggesting RT may augment an immune response and sensitize antigen negative cells to CAR-mediated death in patients with DLBCL.

As it can be observed, different chemotherapy regimens and combination are used, dose in radiation therapy vary between palliative and definitive schedules, timing it is not well defined, so there is a lot of variety in this studies.

Originality in our case is the combination of definitive involved site radiotherapy with chemo (bandamustina) and targeted therapies (polatuzumab/rituximab) with an excellent response maintained and reached in a short period of time. Tolerance was moderate with acute toxicity less than grade 3 and low radiation induced chronic toxicity. We think it is necessary to agree on the use of a scheme for bridging therapy including this combination that seems safe and effective.

Conclusion

The CAR T cell therapy has brought a new hope of treatment for patients with unfavorable evolution of their lymphoma. In many cases, bridging therapy is required, but there is a high heterogeneity and it is not well established. The use of radiation therapy as part of the bridging therapy can help improve palliation and control of the disease. In addition, it might also improve the immune response of CAR-T cells. Combination with biological targets or chemotherapy

might increase tumor radiosensity, but also acute toxicity although it is well tolerated. Prospective studies including this combination should be performed to establish the optimal schedule of bridge therapy.

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