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CAR T-CELL THERAPY IN ULTRA HIGH-RISK AGGRESSIVE B-CELL LYMPHOMA (ABL) PATIENTS WITH TP53 MUTATION

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INTRODUCTION

Intensive regimens (R-mNHL-BFM-90/LBM-04) has significantly improved the results of ABL treatment. However, in 10-15% of patients remains refractory. These patients represent an ultra-high-risk group with no effective 2nd-line chemotherapeutic options available. CAR-T therapy appears to be the only possible option, while experience of its use in this ultra-high-risk group is limited.

AIM

To evaluate the effectiveness of CAR-T in the treatment of ultra-high-risk ABL with mutTP53.

METHOD

From March, 2022 to October, 2023, 4 patients with relapsed or refractory (r/r) ABL received CAR T-cell infusion: No.1 - DLBCL, non-GCB type received 2 cycles of R-mNHL-BFM-90 + lenalidomide with subsequent progression, as second line he received R-DHAP with bendamustine with short-term effect; No.2 –HGBL, NOS with progression after the second cycle of R-mNHL-BFM-90 + venetoclax; No.3 –Burkitt lymphoma, received 4 cycles of LBM-04, one month after the treatment patient had a progression; No.4 –Burkitt lymphoma with CNS involvement (neuroleukemia), tumor lysis syndrome after the first pre-phase injection, ARF; patient received 4 cycles of LBM-04, one month after the end of treatment patient had generalized seizures due to CNS relapse.

All 4 patients had mutations in the TP53 gene, 1 patient - in combination with 17p13 deletion.

RESULTS

In all 4 patients, anti-CD19 CAR-T was obtained 10-12 days after primary T-cell culture collection. Before CAR T-cell infusion, two patients received restraint therapy in combination with targeted drugs as a “bridge”, the patient with neuroleukemia recieved intrathecal administration of cytostatics. Before CAR-T, all 4 patients received standard lymphodepletion (fludarabine, cyclophosphamide), prophylaxis of cytokine release syndrome and neurotoxicity (tocilizumab 600mg, levetiracetam 500mg/day). Before CAR-T, all patients presented signs of disease progression: B-symptoms, increased LDH activity, enlargement of lymph nodes and soft tissue masses, worsening of neurologic symptoms in a patient with neuroleukemia.

Two patients achieved CR, which persisted for +24 and +8 months. One patient had relapse after 3 months. Another one had relapse +11 months after CAR-T infusion. He underwent an allo-HSCT from an HLA-identical brother. Both patients died from disease progression.

Table 1. CAR T-cell therapy efficacy in 4 patients.

	Sex. Years	Diagnosis	Cytogenetics, FISH	TP53	Affected areas	Previous therapy	CAR-T	Results months
1	M.38	DLBCL non-GCB IV st IPI4	-	mut+	Soft tissues of the thigh, pancreas	R-mNHL-BFM-90+ Lenalidomide, DHAP+Polatuzumab vedotin, Ibrutinib	CD19	CR +24
2	M.40	BL III st IPI4	Rearrangement MYC/8q24	mut+	Liver, kidneys, pleura	LBM-04,	CD19	Progression in 3 months
3	M.35	BL IV st IPI4	Rearrangement MYC/8q24	mut+	Stomach, kidney, adrenal glands, pleura, muscle, neuroleukemia	LBM-04, Polatuzumab vedotin, Nivolumab	CD19	CR +11 Relapse
4	M.34	HGBL IVst IPI4	Complex karyotype, t(14;18), MYC ampl	del17p /mut+	Lymphadenopathy, spleen, bone marrow, hyperleukocytosis	R-mNHL-BFM-90 +Venetoclax	CD19	PR +8

CONCLUSIONS

Until recently, allogeneic stem cell transplantation (allo-SCT) remained the only option for ABL patients with refractory disease with mutTP53. Allo-SCT availability is low as most of the patients die within 1.5-2 months because of disease progression before donor immune reconstitution. Short preparation time, no need for restraining therapy and high efficacy makes CAR T-cell therapy the most promising option for ultra-high-risk ABL patients. But the prognosis for relapse of Burkitt's lymphoma remains fatal.

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