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705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Bendamustine Lymphodepletion (LD) Prior to Idecabtagene Vicleucel (Ide-cel) Is Associated with Inferior Outcomes in Relapsed Refractory Multiple Myeloma (RRMM)

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Background

Chimeric antigen receptor therapy (CART) has revolutionized the management of RRMM. LD prior to CART cells modulates the immune environment creating optimal conditions for T cell expansion and subsequent efficacy. Fludarabine/cyclophosphamide (FLU/CY) is an effective LD regimen, and its use has been adopted widely prior to CART cells for all indications. Since the safety of FLU/CY is not established in patients with substantial renal impairment and given recent nationwide fludarabine shortage, alternative lymphodepletion strategies have been explored. Bendamustine (BENDA) has been shown to be a safe alternative with equivalent efficacy and reduced toxicity in non-Hodgkin's lymphoma (NHL). While its use has been extrapolated to RRMM, efficacy and long-term outcomes have not been examined.

Methods

We retrieved and analyzed data on sequential patients (pts) with RRMM treated with commercial Ide-cel at a single institution from its approval in 3/2021 until 5/2023. We captured baseline patient, disease and treatment characteristics. We used IgG (with monoclonal component deducted) and uninvolved FLC as indirect surrogate of CAR-T expansion and on target, off tumor killing of non-malignant plasma cells. We assessed cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS) based on the American Society for Transplantation and Cellular Therapy criteria and disease responses using the International Myeloma Working Group response criteria. We graded hematologic toxicity using the Common Terminology Criteria for Adverse Events version 5.0. We compared efficacy between the cohorts using overall response rate (ORR) and progression-free survival (PFS), since overall survival is expected to be affected by choice of subsequent, often experimental therapies.

Results

We identified 28 pts with RRMM who met the inclusion criteria. Nine pts received alternative LD with BENDA (2 pts - renal dysfunction with creatinine clearance <30ml/min; 7 - fludarabine shortage) and 19 received FLU/CY as LD. Baseline characteristics are summarized in Table. Prior autologous stem cell transplant (ASCT) and prior B cell maturation antigen (BCMA) targeting therapy were more frequent in the FLU/CY cohort. Median absolute lymphocyte count (measured in 10^3/ cmm) prior to LD chemotherapy was similar in both cohorts (0.85 in BENDA vs 0.80 in FLU/CY). Median duration of absolute neutrophil count <1,000/μL was shorter in the BENDA cohort. The incidence of any grade CRS (56% vs. 90%, p=0.06) and tocilizumab use (56% vs. 84%, p=0.16) was lower with BENDA compared to FLU/CY. In the absence of ide-cel expansion data, we used nadir polyclonal IgG and uninvolved free light chain (uFLC) in the initial 90 days post CART cell infusion as surrogate of non-malignant plasma burden and therefore ide-cel expansion. We noted lower median uFLC and median IgG with FLU/CY vs. BENDA. The overall response rate was lower with BENDA (22%) vs. FLU/CY (79%, p=0.01). With median follow up of 4.8 mo., all pts in the BENDA cohort progressed with median PFS of 1.6 months vs 7.8 months for FLU/CY (p<0.001, Figure). The median OS for both cohorts is not yet reached.

Conclusion:

BENDA LD prior to ide-cel infusion results in suboptimal lymphodepletion and subsequent inferior outcomes including low rate of objective responses and decreased progression free survival. The inferior efficacy of BENDA as LD likely results from inferior ide-cel expansion and persistence resulting in less frequent and severe CRS and cytopenias and less suppression

of unaffected immunoglobulins. Future efforts to study alternative lymphodepletion approaches is essential given inability to use fludarabine in patients with severe renal dysfunction and periods of critical drug shortages. While there is a need to develop alternatives for LD prior to ide-cel, BENDA is an inadequate substitute of FLU/CY.

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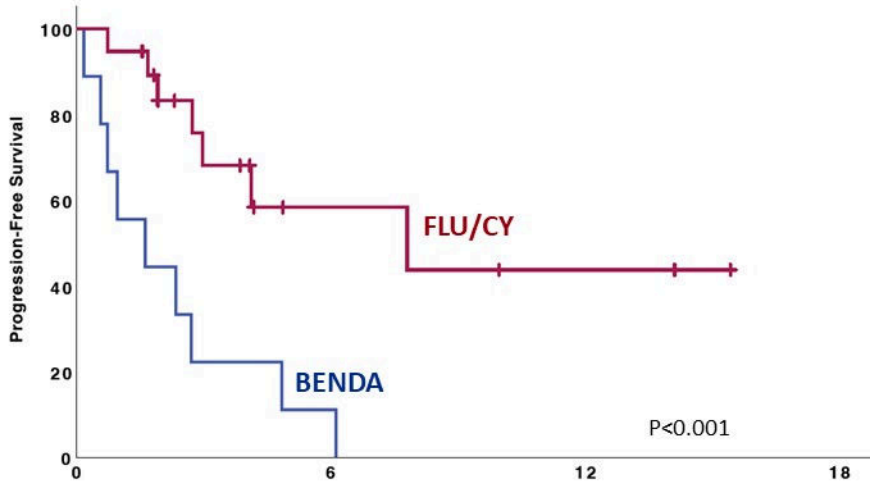
Baseline and treatment characteristics	BENDA (N=9)	FLU/CY (N=19)
Patient Characteristics		
Age, median in years	69 (IQR 58-73)	66 (IQR 61-75))
Male (%)	6 (67)	16 (84)
Racial/ethnic minorities (%)	4 (44)	10 (53)
Disease/Treatment characteristics		
Median prior lines of therapy (range)	5 (4-7)	4 (3-9)
Prior ASCT (%)	5 (56)	17 (90)
Prior BCMA-directed therapy (%)	0 (0)	4(21)
Median cell dose (x 10^6)	408 (IQR 363.09-440)	431 (IQR 384-448)
Median lymphocyte count prior to LDC (per µliter)	0.85 (IQR 0.45-1.4)	0.80 (IQR 0.41-1.4)
Toxicity Characteristics		
CRS (%)	5 (56)	17 (90)
Tocilizumab use (%)	5 (56)	16 (84)
Corticosteroid use (%)	2 (22)	7 (37)
ICANS (%)	2 (22)	4 (21)
Median duration of≥Gr3 neutropenia in days	0 (IQR 0-5)	21 (IQR 13-54)
Surrogates of non-malignant plasma cell suppression		
Median nadir uFLC by 90 days in mg/l	3.4 (IQR 1.4-5.0)	1.4 (IQR 1.4-1.5)
Median nadir IgG by 90 days in mg/dl	433 (IQR 270-481)	256 (IQR 175-509)



Number at risk (number censored)				
BENDA	9 (0)	1 (0)	0 (0)	0 (0)
FLU/CY	19 (0)	4 (9)	2 (10)	0 (12)

Figure 1

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