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EFFECTIVENESS AND SAFETY OF BISPECIFIC ANTIBODIES TARGETING BCMA AND CD3 IN PATIENTS WITH CENTRAL NERVOUS SYSTEM MULTIPLE MYELOMA (CNS-MM): IFM 2023-06, A RETROSPECTIVE COHORT STUDY.

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INTRODUCTION

Multiple Myeloma with Central Nervous System involvement (CNS-MM) is a rare but aggressive form of extramedullary disease characterized by plasma cell infiltration of the CNS, leptomeninges or cerebrospinal fluid (CSF) which has a very poor prognosis (1,2).
Patients with triple-class exposed and/or refractory MM can receive since 2022 bispecific antibodies targeting BCMAxCD3. Specific toxicities of these new agents include Immune effector cell-associated neurotoxicity syndrome (ICANS). CNS-MM patients were typically excluded from clinical trials; due to the few data and the neurological risk at the initiation of bispecifics, the use of these new immunotherapies in CNS-MM is challenging.

AIM

We report safety and efficacy data from RRMM patients with CNS involvement at relapse treated with teclistamab or elranatamab.

METHOD

The IFM2023-06 study is an observational retrospective multicentric cohort including RRMM patients with CNS involvement treated with teclistamab or elranatamab in the French Early Access programs.

CNS involvement was defined by the presence of plasma cells in the CSF (proven CNS-MM) or by an highly compatible imaging. Both teclistamab and elranatamab were prescribed according to their respective marketing authorization.

Patients were informed of their right to oppose to the use of their data, and study was submitted to the French Health Data Hub.

RESULTS

Patients characteristics (table 1)
Between Dec 2022 and Feb 2024, 9 CNS-RRMM patients were treated with teclistamab (n=8) or elranatamab (n=1) in French hospitals. The median age was 63 y, the sex ratio 2. Light chain MM were the most frequent (44%) and HR cytogenetics were identified in 3/9 (33%) patients.
An additional EMD was frequently identified (5/8 evaluable patients) and could concern lymph nodes (3/8), kidney, liver, pleura and/or subcutaneous tissues.

Neurological features (table 1)
Clinical manifestations included chin hypoesthesia in 66% of cases (6/9), oculomotor paralysis in 33% (3/9), lethargy/confusion in 33% (3/9).
A CSF analysis was performed in 8 pts and was abnormal in all cases (constant hyperproteinorachia); clonal plasma cells were identified in 7/8 cases.
Brain MRI was carried out in all 9 patients and was abnormal in 3 (33%): 2 had a pachymeningitis and 2 intraparenchymal lesions.

Bispecific step-up dosing
Step-up dosing was classic for 8/9 patients. For the last patient who presented a grade 2 CRS and a grade 2 ICANS, the teclistamab full dose was reached within 18 days.

Associated treatments
3 patients received additional treatment: radiotherapy (1), methotrexate IT (1) and thiotepa IT(1).

Safety profile (table 2)
Grade 1 or 2 Cytokine release syndrome (CRS) occurred in 5/8 pts (exclusively during the step-up dosing) and was treated with tocilizumab for 2 pts, with dexamethasone for 1 ; no grade 3-4 was reported. Grade 2 ICANS occurred in one patient, treated with dexamethasone.
Nearly half of the patients (4/9) experienced grade 2 or more infections despite primary prophylaxis. One patient died during step-up due to sepsis.

TABLE 1	
Baseline characteristics	number (%)
Median age (range)	63 (50-79)
Sex	
Men	6 (66%)
Women	3 (33%)
Immunoglobulin subtype	
light chain	4 (44%)
Ig A	3 (33%)
Ig G	2(22%)
Cytogenetics	
no high risk or NA	6 (66%)
high risk	3 (33%)
Median number of previous lines (range)	3 (2-5)
Extramedullary disease	5/8 (62%)
CSF abnormalities	8/8 (100%)
Hyperproteinorachia	8/8 (100%)
Clonal plasma cells	7/8 (87%)
Brain MRI abnormalities	3/8 (37%)

TABLE 2		
Prophylaxis and safety		
Antimicrobial prophylaxis		
Amoxicillin	4/9 (44%)	
Cotrimoxazole	9/9 (100%)	
Valacyclovir	9/9 (100%)	
Polyvalent immunoglobulins	6/9 (66%)	
CRS	5/9 (55%)	
grade >2 CRS	1/9 (11%)	
ICANS	1/9 (11%)	
grade >2		0%
Grade 2 or more infections	4/9 (44%)	
grade 5	1/9 (11%)	

Response

Taking precautions when interpreting results, 3 patients (33%) responded and presented, in parallel of a systemic response related to bispecific treatment, a neurological improvement. One of them disclosed systemic CR and neurological response during 13 months before relapse. One presented systemic PR and full neurologic improvement during 3 months before relapse and death. One is still in CR and neurological response after 2 months with ongoing bispecific treatment.

Nor radiotherapy neither thiotepa demonstrated efficiency. No response was observed in the patient with ICANS.

CONCLUSIONS

Despite a limited cohort, the use of anti-BCMA bispecific antibodies seem to be feasible and safe for patients with CNS-RRMM. The incidence of CRS, ICANS, infections appears to be comparable with those seen in clinical trials. More data and follow up are needed to describe the clinical benefit and medium term outcome.

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