Received: 25 January 2025 | Accepted: 30 April 2025

DOI: 10.1111/bjh.20143

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

RESEARCH LETTER

Monoclonal gammopathy of undetermined significance in patients with solid tumours: Effects of immune checkpoint inhibitors on the monoclonal protein

To the Editor,

Immune checkpoint inhibitors (ICIs) have been incorporated in the management of both solid tumours and haematological malignancies, leading to prolonged survival.[1] Immune checkpoint blockade overcomes the tumour-mediated immune inhibition and blocks the immunosuppressive signalling that is induced by the expression of ligands on cancer cells.[2,3] Currently, there is no approval of ICIs for multiple myeloma (MM).

MM originates from a premalignant state known as monoclonal gammopathy of undetermined significance (MGUS) or smouldering multiple myeloma (SMM). This evolution is linked to immune evasion through the upregulation of inhibitory ligands to immune checkpoints leading to loss of T-cell function.[4] There is evidence that programmed cell death ligand 1 (PD-L1) expression is upregulated in MM cells compared to MGUS.[4,5] Furthermore, T cells and natural killer (NK) cells in MM show increased levels of programmed cell death protein 1 (PD-1), whereas progression from MGUS to MM has been associated with a decline in NK cell cytotoxicity.[6] Progressive impairment of T-cell function from MGUS to MM may contribute to disease evolution. Given the immunoparesis in MM and the finding that T-cell exhaustion is established early in patients with MGUS, there is a rationale for the potential role of administration of ICIs in MGUS to prevent or delay evolution. However, available data are scarce.

We have previously shown that chemotherapy with a taxane and a platinum analogue in patients with solid tumours resulted in a modest reduction of monoclonal protein levels.[7] However, irinotecan-based chemotherapy resulted in a marked reduction of the serum monoclonal protein.[7] Taking all the above into consideration, we aimed to evaluate the impact of ICIs on the kinetics of the serum monoclonal component of MGUS in cancer patients receiving ICIs for the treatment of solid tumours. Although the results from early phase studies evaluating ICIs' monotherapy in patients with symptomatic MM did not show particularly promising results, we wanted to evaluate whether there may be an effect of these agents in individuals with precursor plasma cell dyscrasias, where the function of T cells may be better preserved than later in the course of the disease.

We prospectively evaluated all consecutive patients with solid tumours that were treated with PD-1/PD-L1 inhibitors as monotherapy for all cancer indications during a 5-year period (November 2018–November 2023) in a single institution. No formal power calculation was conducted a priori. ICIs were administered per approved indication until disease progression, unacceptable toxicity or death. A workup for monoclonal gammopathies was performed at baseline before treatment initiation with serum immunofixation and electrophoresis.

MGUS was defined as follows: (1) serum monoclonal spike of less than 3 g/dL and (2) absence of any end organ damage.[8] Patients diagnosed with MGUS were followed with serum immunoelectrophoresis, serum free light chains, haematology and biochemistry exams at cycles 2, 4, 6 and 8 posttreatment initiation. A written informed consent was obtained from all patients. The study has been performed in accordance with the 1964 Helsinki Declaration and has been approved by the Institutional Review Board of Alexandra University Hospital.

A total of 120 previously untreated patients with solid tumours who received monotherapy with PD-1/PD-L1 inhibitors were included. Fourteen patients ($n = 14$) (12%) were diagnosed with MGUS (Table 1). Median age was 68 years (range: 55–82). In all, 12 patients were males (86%) and two were females (14%). Among the patients diagnosed with MGUS, the primary tumour was bladder cancer in six patients, lung cancer in four patients, renal cancer in three patients and ampullary adenocarcinoma in one patient. Median baseline M-peak value was 0.67 g/dL (range: 0.24–2.54). Six patients (43%) received pembrolizumab, six patients nivolumab (43%), one patient avelumab and one durvalumab. All 14 patients diagnosed with MGUS received at least two cycles of immunotherapy. Bone marrow biopsy was conducted in nine patients. None of the patients had more than 10% plasma cells in the bone marrow.

All patients with MGUS had a follow-up time of at least 8 months from the baseline measurement of the M-protein. Testing for differences between baseline M-peak and M-peak

TABLE 1 Baseline characteristics of the 14 patients diagnosed with MGUS and treated with ICIs.

Case	Primary tumour	Baseline M-peak (g/dL)	Immunofixation type	PD-1/PD-L1 inhibitors	M-peak at cycle 2	M-peak at cycle 4	M-peak at cycle 6	M-peak at cycle 8
64M	Bladder	0.24	IgMκ	Nivolumab	0.26	0.24	0.23	0.19
58M	Ampullary	1.4	IgAλ	Pembrolizumab	0.92	1.53	0.99	1.00
82F	NSCLC	0.55	IgGκ	Durvalumab	0.55	0.57	0.54	0.59
81M	NSCLC	0.2	IgAκ	Pembrolizumab	0.23	0.21	0.2	0.24
72M	Bladder	0.46	IgGκ	Pembrolizumab	0.41	0.49	0.44	0.39
64M	RCC	1.14	IgGκ	Nivolumab	1.11	1.10	1.19	1.02
66M	RCC	0.44	IgGκ	Nivolumab	0.41	0.40	0.45	0.39
76M	Bladder	1.18	IgGκ	Pembrolizumab	0.56	0.73	0.79	0.91
65M	RCC	0.72	IgGλ	Nivolumab	0.64	0.59	0.61	0.55
75F	NSCLC	0.27	IgGκ	Pembrolizumab	0.26	0.31	0.30	0.32
67M	Bladder	1.69	IgGκ	Avelumab	1.70	1.81	1.59	1.75
55M	NSCLC	1.52	IgGλ	Nivolumab	1.78	1.79	2.2	2.5
76M	Bladder	2.54	IgGκ	Pembrolizumab	2.41	2.61	2.71	2.44
68M	Bladder	0.61	IgGκ	Nivolumab	0.69	0.74	0.73	0.63

Abbreviations: F, female; ICIs, Immune checkpoint inhibitors; Ig, immunoglobulin; M, male; MGUS, monoclonal gammopathy of undetermined significance; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RCC, renal cell carcinoma.

at each time point was performed by utilising the Wilcoxon signed-rank test. No statistically significant differences between the baseline and the subsequent M-peak levels at the second ($p = 0.263$), fourth ($p = 0.363$), sixth ($p = 0.967$) and eighth cycle ($p = 0.209$) after treatment initiation were observed.

Overall, MGUS was detected in 12% of patients with solid tumours, comparable to the general population.[9,10] We observed no reduction in the monoclonal protein after the administration of ICIs, even at eight cycles posttreatment initiation, including one patient with immunoglobulin M (IgM) MGUS.

Previous studies have shown that PD-1 inhibitor monotherapy has poor efficacy in treating symptomatic MM. Phase 1 trials of both nivolumab and pembrolizumab demonstrated an overall response rate of 4% and 0% respectively.[11,12] To date, there has been no study evaluating PD-1/PD-L1 inhibitors in patients with MGUS. However, the role of pembrolizumab was previously assessed in 13 patients with intermediate-/high-risk SMM.[13] Among them, one patient achieved complete remission (7.7%), 11 had stable disease (84.6%) and one progressed to symptomatic disease.[13] Furthermore, the majority of clinical trials evaluating PD-1/PD-L1 inhibitors in combination with anti-myeloma treatments have been terminated due to futility.[14] The combination of durvalumab with daratumumab in patients with daratumumab-refractory MM was evaluated in a prospective phase 2 clinical study (NCT03000452), but no patient responded.[15] The combination of pembrolizumab with either pomalidomide–dexamethasone or lenalidomide–dexamethasone also failed to show significant benefit in the KEYNOTE-183 and KEYNOTE-185 trials.[14] Finally, the benefit–risk ratio of pembrolizumab plus lenalidomide–dexamethasone was unfavourable for patients with newly diagnosed MM.[16]

MGUS and MM are heterogeneous entities with often competing subclones co-present; thus, immune responses among patients may be heterogeneous as well. Over time, a subset of patients with MGUS experience gradual increases in M-protein levels, reflecting a higher risk of progression to MM or related disorders. However, the majority maintain a stable or only slightly increasing M-protein concentration over years of follow-up. The rate of progression varies depending on several factors, including initial M-protein level, type of immunoglobulin and presence of abnormal serum free light chains.[17] Our aim was to evaluate any potential decrease in M-protein with the administration of PD-1/PD-L1 inhibitors. Any potential change in the levels of M-protein would be anticipated during the first 6 months of treatment, taking into consideration the M-protein kinetics with anti-myeloma treatments in patients with SMM.[11,12] The effect on disease evolution to symptomatic disease would necessitate longer follow-up. However, the reason for the lack of response to ICIs compared with other tumours may derive from the immunosuppressive nature of the MM microenvironment. The immunodeficiency associated with MM may lead to decreased response to treatment with PD-1 inhibitors. Both T-cell intrinsic (e.g. exhaustion, senescence) and extrinsic (e.g. Tregs, stromal inflammation) mechanisms promote immune suppression. In addition, MM induces both innate and adaptive immune dysregulation through many independent mechanisms. Other potential therapeutic targets, such as Cytotoxic T-lymphocyte associated protein 4 (CTLA-4), Lymphocyte-activated gene 3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), and T-cell immunoglobulin and ITIM domain (TIGIT) are involved in the inhibition of T-cell functions associated with myeloma development as well. Consequently, the inhibition of multiple pathways may be suitable. Dual inhibition of PD-1 and CTLA-4 pathways with nivolumab plus

ipilimumab as consolidation therapy post-transplant in patients with high-risk MM achieved a 57.1% progression-free survival rate and an 87% overall survival rate at 18 months.[18] Currently, drugs targeting the killer immunoglobulin-like receptors, a family of cellular receptors that are expressed on NK cells, V-domain immunoglobulin suppressor of T-cell activation and TIGIT have gained ground in MM as monotherapy or in combination with monoclonal antibodies or proteasome inhibitors.[19] Furthermore, preclinical data suggest that the addition of anti-PD-1 to chimeric antigen receptor-T (CAR-T) cell therapies may increase the anti-tumour effect by overcoming the immunosuppressive microenvironment and reducing CAR-T cell apoptosis. A phase 2 study (NCT04162119) explores the safety and efficacy of B-cell maturation antigen (BCMA)-PD1-CAR-T cells in relapsed/refractory MM.[20]

Among the limitations of our study, we should note that the low number of patients with MGUS, the absence of a priori power calculations and the limited follow-up should be kept in mind when generalizing and interpreting the results of the study. Nevertheless, as a hypothesis-generating study, the results do not indicate any effect of ICIs on the levels of M-protein. Only one patient in our study had IgM MGUS, who did not show any change in M-protein with nivolumab. Due to the distinct underlying aetiology, it would be interesting to further evaluate a larger cohort of these patients in future studies.

In conclusion, our data indicate that treatment with anti-PD-1/PD-L1 antibodies does not affect the monoclonal protein kinetics in patients diagnosed with MGUS. Despite the methodological limitations, our results confirm that single-agent activity of ICIs is rather unpromising in patients with monoclonal gammopathies and novel immunological targets are essential to be determined.

AUTHOR CONTRIBUTIONS

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KEYWORDS

ICIs, immune checkpoint, immunotherapy, MGUS, monoclonal protein, multiple myeloma

ACKNOWLEDGEMENTS

The authors have nothing to report.

FUNDING INFORMATION

This research received no external funding.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Further supporting data are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The study has been performed in accordance with the 1964 Helsinki Declaration and has been approved by the Institutional Review Board of Alexandra University Hospital.

PATIENT CONSENT STATEMENT

A written informed consent was obtained from all patients included in this study.

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