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Immune checkpoints inhibitors for solid tumours after allogeneic haematopoietic stem-cell transplantation: About four clinical cases

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Immunotherapy, and particularly immune checkpoint inhibitors (ICI), represents one of the best advances in oncology in the last decade. Drugs which block the immune checkpoints (mainly PD-1/PD-L1 and CTLA-4) pathway have shown durable objective responses for advanced various solid malignancies including melanoma [1–3] and non–small cell lung carcinoma [4–6]. CTLA-4 is a negative regulator of T-cell activation [7], which can be inactivated by ipilimumab, a recombinant human monoclonal antibody that avoids CTLA-4 binding to its ligand. Nivolumab and pembrolizumab are human monoclonal antibodies that block the interaction between programmed cell death protein 1 receptor (PD-1) and its ligands (PD-L1 and PD-L2) leading to a decrease in PD-1–mediated inhibition of the immune response [8]. CTLA-4 and PD-1 pathways are also involved in limiting excessive T-cell activation and prevention of auto-immunity [9]. Allogeneic haematopoietic stem-cell transplantation (AHSCT) is an option to treat high-risk or refractory haematological malignancies. Acute and chronic graft versus host diseases (GVHD) are the main adverse events linked to this therapy. Immunological mechanisms of GVHD are in part related to PD-L1 expression level on donor T cells in murine models [10], and one case of lethal GVHD after PD-1–inhibitor treatment for refractory Hodgkin disease has recently been published [11]. We wondered how ICI could be safe and efficient after AHSCT for a haematological malignancy. We report here four cases of patients diagnosed with secondary solid cancer after AHSCT and treated with ICI (see Table 1).

1. Clinical case 1

A 52-year-old man treated for a refractory mantle cell lymphoma displayed acute and chronic GVHD after AHSCT which was successfully treated with corticosteroids. Five years later, he was diagnosed with stage IV metastatic lung adenocarcinoma with *KRAS* mutation. He successively received a platinum-based doublet followed with pemetrexed maintenance. After chemotherapy failure he received nivolumab for 1 month.

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Table 1
Main clinicopathological features related to previous haematological disease, solid tumour, as well as immune checkpoint inhibitor therapy.

Clinicopathological features	Patient-01	Patient-02	Patient-03	Patient-04
Haematological disease	Mantle cell lymphoma	Acute myeloid leukaemia type 6	Mantle cell lymphoma	Chronic lymphocytic leukaemia
Acute GVHD	Cutaneous	Digestive	Cutaneous and hepatic	None
Chronic GVHD	Cutaneous	Mucous	Cutaneous and hepatic	Cutaneous and digestive
GVHD treatment	Steroids	Mycophénolate mofétil	Steroids	Steroids; ciclosporin
Delay between AHSCT and solid tumour diagnosis	5 years	7 years	9 years	6 years
Smoking history	50 PY (stopped at 40 years)	30 PY (stopped at 53 years)	25 PY (stopped at 52 years)	NA
Tumour type	Metastatic lung adenocarcinoma	Metastatic lung adenocarcinoma; bladder cancer	Metastatic lung adenocarcinoma	Melanoma
Molecular alteration	KRAS mutation	None	None	None
Type of immunotherapy	Nivolumab	Nivolumab	Nivolumab	Pembrolizumab, ipilimumab and nivolumab
IrAE	None	None	None	Fulminant type 1 diabetes
Treatment duration	1 month	3 months	Ongoing after 6 months of follow-up	Adjuvant pembrolizumab: 6 months; ipilimumab: 3 months; nivolumab: 4 months
Cause of treatment discontinuation	Early cerebral progression	Hepatic and pleural progression	NA	Cerebral and systemic progression

GVHD, graft versus host disease; AHSCT, allogeneic haematopoietic stem-cell transplantation; NA, non-assessable; IrAE, immune-related adverse event.

Nivolumab was stopped because of cerebral progression requiring corticosteroids, but without any adverse event. He finally died of pneumocystis pneumonia a few months later.

2. Clinical case 2

A 66-year-old man received an AHSCT for a refractory acute myeloid leukaemia (AML-6). He presented acute and chronic GVHD, successfully treated with mycophenolate mofetil. Seven years later, he was diagnosed with stage IV metastatic lung adenocarcinoma, without any molecular alteration. He experienced disease progression after one line of platinum-based chemotherapy and was concomitantly diagnosed with a bladder cancer. He received nivolumab after lung cancer progression. Even though he had no adverse event under nivolumab, immunotherapy was discontinued after 3 months because of multi-metastatic progression of lung cancer and likely bladder cancer.

3. Clinical case 3

A 52-year-old man received an AHSCT for a refractory mantle cell lymphoma and presented acute and chronic GVHD requiring corticosteroids. Nine years later, he was diagnosed with a localised (T2N0M0) poorly differentiated lung adenocarcinoma and underwent surgery. He presented a metastatic relapse 6 months after surgery treated with induction chemotherapy (platinum, pemetrexed and bevacizumab combination) followed by continuation maintenance (pemetrexed and bevacizumab combination) during 3 months. Because of disease progression, he received nivolumab, which is still ongoing with no adverse event. computed tomography-scan at 6 months showed a partial response.

4. Clinical case 4

A 42-year-old man received an AHSCT for a chronic lymphocytic leukaemia, with subsequent chronic cutaneous and digestive GVHD treated with steroids and ciclosporin. Six years later a scalp subcutaneous metastasis of melanoma, with no *BRAF* and *NRAS* mutations was resected. The primary melanoma could not be identified. One year later a cervical node was surgically resected and the patient was enrolled in an adjuvant clinical trial assessing the efficacy of pembrolizumab versus placebo. The treatment was stopped after 6 months because of disease progression. He received ipilimumab for four injections without efficacy and then started a second line of treatment with nivolumab. Two months after he was diagnosed with fulminant type 1 diabetes, nivolumab was maintained for 2 months despite this adverse event before a cerebral and systemic progression was observed. The patient died few weeks later.