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Review

Optimal management of immune-related toxicities associated with checkpoint inhibitors in lung cancer

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ABSTRACT

Antibodies against immune checkpoints including CTLA-4, PD-1 and PD-L1 are increasingly being used in lung cancer. They are associated with novel, immune related toxicities not previously encountered with established treatments for lung cancer including colitis, hepatitis, rashes, neuropathies and other rarer immune mediated toxicities. Although generally these are low grade, there is a potential to be life threatening if not managed promptly. Early recognition of toxicity and institution of management algorithms are key to ensuring patient safety. We review the common toxicities and provide recommendations on their management.

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1. Background

Cytotoxic chemotherapy and targeted therapies have improved outcomes for lung cancer patients. Survival in early stage non-small cell lung cancer (NSCLC) is improved with adjuvant chemotherapy and, when combined with radiotherapy, improves survival in stage III inoperable NSCLC and small cell lung cancer (SCLC) [1,2]. In the palliative setting chemotherapy can provide symptom relief and survival benefit [1,3]. Targeted therapies against the epidermal growth factor receptor (EGFR) have improved outcomes for the subgroup of NSCLC bearing an activating EGFR mutation [4,5]. In addition, tumours with the anaplastic lymphoma kinase (ALK) gene rearrangement can be effectively targeted with crizotinib [6]. Despite advances improved outcomes have been modest.

Recent progress in checkpoint inhibition of the immune system has translated into major therapeutic advances in the treatment of metastatic melanoma and has significant implications for a number of other cancers including lung cancer. Both tumour types have a very high incidence of exomic mutations related to established carcinogens, and this results in neoantigens that activate the immune system [7]. The CTLA-4 inhibitor ipilimumab is associated with a long-term survival benefit in a minority of melanoma patients and is approved for first and subsequent line treatment of advanced melanoma. Ipilimumab is currently not licensed for the treatment of lung cancer. The results of early phase studies in both SCLC and NSCLC suggest a survival benefit when given with chemotherapy compared to chemotherapy alone. Results of pivotal phase III trials are awaited.

Inhibitors of PD-1 or PD-L1 allow cancers to be destroyed by the immune system by inhibiting cell surface proteins that tumour cells and tumour infiltrating myeloid cells can express to inactivate T-lymphocytes. These drugs are associated with high response rates and expectations of long-term survival for some patients. The Keynote 001 study of pembrolizumab, a PD-1 inhibitor, showed a response rate of 24–40% and 1-year survival of 71% in metastatic melanoma patients [8]. A randomised phase 3 study comparing another PD-1 inhibitor, nivolumab, with investigators choice chemotherapy (ICC) after failure of ipilimumab demonstrated higher response rates with nivolumab (51% vs 35%). This was despite a higher incidence of adverse prognostic factors in the nivolumab arm [9].

A randomised phase 3 study of nivolumab 3 mg/kg 2-weekly vs DTIC 1000 mg/m^2 3-weekly in treatment naïve melanoma patients also demonstrated nivolumab to be superior to chemotherapy for overall response rate (40.0% vs 13.9%; $P<0.001$), median progression-free survival (5.1 vs 2.2 months; $P<0.001$), and 1 year overall rate of survival (72.9% vs 42.1%; $P<0.001$) [10]. The results of other pivotal first line studies are awaited, but these agents are very likely to become a standard of care for patients with melanoma.

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Table 1
Incidence of higher grade toxicity with ipilimumab, anti-PD-1 and anti-PD-L1 therapy.

	Ipilimumab [17,18] (10 mg/kg and 3 mg/kg doses)		Anti-PD-1 [29] (3 mg/kg)	Anti-PDL-1 [22] (total for all dose ranges 0.3–10 mg/kg)
	Grade 3 (%)	Grade 4 (%)	Grade 4 (%)	Grade 3 or 4 (%)
Any irAE	12–31	2–10	1–2	5
Skin	1.5–2		<1	0
Pruritus	0–2	<1	0	0
Rash	1	0	0	0
Vitiligo	0	0	0	0
Gastrointestinal	8		<1	0
Diarrhoea	4–5	1	0	0
Colitis	1–5	0–1	<1	0
Endocrine	1–2	1–2	0–2	0
Hypothyroidism	<1	<1	0–2	0
Hyperthyroidism	0	0		0
Hypopituitarism	<1	<1	<1	0
Hypophysitis	<1	0	0	0
Adrenal insufficiency	0	0	0	<1
Hepatitis	1	<1	0	0
Pneumonitis	0	0	0	0

Studies in lung cancer are not as far advanced. A large phase 1 study of nivolumab in 122 heavily pre-treated patients with NSCLC observed 14 objective responses, seen in both squamous and non-squamous subtypes [11]. Nivolumab is currently under investigation in phase 3 trials for treatment naive and previously treated patients (NCT02041533, NCT02066636) [12]. Pembrolizumab has also been investigated in early phase studies of lung cancer patients both as a single agent and in combination with cytotoxic chemotherapy [13]. Response rates of 20–33% have been reported [13]. It is currently being studied against standard of care chemotherapy in later phase trials (11, NCT01905657).

2. Immune related toxicity

The spectrum and mechanism of toxicity related to immune checkpoint inhibition is autoimmune in nature and distinct to that of other cancer therapies [14]. The incidence of ipilimumab and PD-1 inhibitor toxicity by organ system are outlined in Table 1 [7,15].

A pooled analysis of ipilimumab studies demonstrated that approximately two-thirds of patients experienced an immune related adverse event (irAE) with the majority being grade 1 and 2 [16]. Most commonly reported irAEs were gastrointestinal (GI) and dermatological. Less common toxicities included endocrine, hepatic and neurological. Toxicity-related death occurred in less than 1% of cases [16]. Toxicity related to ipilimumab appears to be dose related. A phase 2 study identified an increased response rate and higher rate of irAE with increased dose [14]. This is important because studies of ipilimumab in lung cancer have used the higher 10 mg/kg dose of ipilimumab.

For ipilimumab, timing of onset of irAEs is dependent on the organ system involved; dermatological effects tend to occur first within 2–3 weeks, gastrointestinal after 6–7 weeks and endocrine later at around 9 weeks [19]. Most IrAEs occur within 3 months of commencing therapy but late toxicity after treatment discontinuation can occur [20].

Toxicity with anti-PD-1 antibodies is less common but can also be potentially fatal. The most common irAEs experienced with nivolumab and pembrolizumab are rash, pruritus and diarrhoea, the majority of which are low grade [11,13]. In a phase 1 study of nivolumab, irAEs also included vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. Grade 3 or 4 pneumonitis was noted in 1% of patients. Two drug related deaths were due to pneumonitis in lung cancer patients. Early grade pneumonitis was noted in 2% of patients and was reversible with discontinuation of nivolumab and initiation of steroids [11]. A phase 1 study of nivolumab combined with chemotherapy reported pneumonitis in 7% of cases [21].

Anti-PD-L1 antibodies have also been well tolerated. A phase 1 study treated 207 patients with a variety of tumour types with escalating doses of anti-PD-L1 antibody [22]. Grade 3 or 4 toxicity was seen in 9% of patients and the most common adverse events were fatigue, infusion reactions, diarrhoea, arthralgia, rash, nausea, pruritus, and headache. There were no cases of pneumonitis reported and no deaths attributed to toxicity [22].

3. Managing immune related adverse events

A critical first step in managing irAEs is awareness of this class of toxic effect and requires education of the multi-disciplinary team. Patient education about potential side effects and appropriate steps to take is also critically important to ensure early recognition and treatment of irAEs. There is evidence that early intervention reduces both the maximum severity and duration of irAEs [23].

The severity of toxicity should be graded using the Common Terminology Criteria for Adverse Events (CTCAE). CTCAE grade 1 and 2 toxicity can often be managed with supportive care and increased monitoring. Higher grades require interruption of immunotherapy and commencement of high dose corticosteroids. There is no role for dose reductions. The route and choice of corticosteroid will depend on the severity of irAE and will be discussed. In addition to immunosuppression, most patients will require supportive management and treatment of secondary complications. Table 2 outlines a general management algorithm for irAEs.

4. Gastrointestinal

4.1. Colitis

The impact on the gastrointestinal system reported with the use of immunotherapy has been associated with death due to bowel perforation. In phase 3 studies of ipilimumab in metastatic melanoma, total rates of diarrhoea were 27.5% (3 mg/kg) and 32.8% (10 mg/kg) and rates of colitis 7.6% and 4.5% respectively [17,18]. Typically diarrhoea tends to commence around 6–7 weeks following commencement of treatment [19]. Bloody diarrhoea may be an indication of more severe colitis but is uncommon.

At colonoscopy, colitis usually affects the distal colon with sparing of the rectum. Macroscopic abnormalities include erythema, oedema, erosions, and bleeding. In severe cases microscopic findings include neutrophil invasion, destruction of surface epithelium and crypts, and crypt microabcesses [20]. Immune infiltrate

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