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Liver toxicity in the era of immune checkpoint inhibitors: A practical approach☆

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ABSTRACT

Immune checkpoint inhibitors have revolutionized the cancer treatment with an approved efficacy in different solid tumors and hematologic malignancies. These agents are increasing the indication in cancer treatment, but can be associated with serious immune-related adverse effects (IRAEs). Dermatologic and gastrointestinal toxicities are the most common IRAE followed by endocrinopathies with a different time of occurrence. Rarely cases of gastrointestinal toxicities are observed almost 2 years after initiation of the therapy. In this review we focus on liver toxicity related to these immunotherapeutic agents for which the largest amount of safety data is available. The management of drug-induced liver toxicity is very complicated and in same cases may take a long period of time to be resolved. A prompt recognition of liver IRAEs and an appropriate management of this event, requiring close collaboration with other specialist figures, could improve its treatment with evident implication on the efficacy of the therapy.

1. Introduction

In the last decade, immunotherapy went from a constituent of tumors to a mainstay in the cancer treatment. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), the programmed cell death protein 1 (PD-1) and its ligands (PD-L1/PD-L2) as well as several new generation checkpoint inhibitors have proven to modulate the immune response towards cancer clearance among a variety of human malignancies and many have reached a solid placement in routine clinical practice.

CTLA-4 is a co-inhibitory receptor expressed on $CD4^+$ and $CD8^+$ T cells in early stage of T-cell activation. This receptor binds with high affinity to B7 and can compete with CD28 to further inhibit T cell activity. The binding of CTLA-4 with B7, in fact, stops the T cell from maintaining an immune response with subsequent downregulation of T helper cell (Thelp) and enhancement of regulatory T cells (Treg) immunosuppressive activities (Krummel et al., 1996; Chambers et al., 1996) Ipilimumab, a fully human IgG1 monoclonal antibody against CTLA-4, was the first checkpoint inhibitor approved for malignant melanoma (Hodi et al., 2010).

The PD-1 pathway, differently from CTLA-4 - which functions mainly in the lymph nodes -, operates in the tumor microenvironment (TME). PD-1 is a protein activated on T and B cells, natural killers (NK) and antigen-presenting cells (APC) (Keir et al., 2008). This protein interacts with PD-L1 and PD-L2 present on the surface of tumor cells as well as on the infiltrating immune milieu, including tumor associated macrophages (TAMs), dendritic cells (DC), fibroblasts, and activated T cells (Freeman et al., 2000; Dong et al., 2002; Blank et al., 2004). The binding of PD-1 with its ligands enhances T cell function, blocking T cell exhaustion and licensing for anti-tumor activity (Okazaki and Honjo, 2007; Zou and Chen, 2008; Chow, 2013). Pembrolizumab is a monoclonal antibodies targeted against PD-1, approved as first line for patient affected by non small cell lung cancer (NSCLC) expressing high levels of PD-L1 ($\geq$50%) (Reck et al., 2016) and in second and beyond lines in tumors expressing any PD-L1($\geq$1%) (Herbst et al., 2016). Nivolumab is another monoclonal antibody targeted against PD-1 and currently approved for NSCLC in the second and beyond lines (Borghaei et al., 2015; Brahmer et al., 2015). Atezolizumab is the first monoclonal antibody targeted against PD-L1 and received approval for the treatment of advanced urothelial carcinoma and metastatic NSCLC in the second-line setting and beyond, both by the end of 2016 (Bellmunt

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et al., 2017; Rittmeyer et al., 2017; Lee et al., 2017). Durvalumab, another anti-PD-L1, has also recently being approved for the treatment of patients with metastatic urothelial carcinoma (Powles et al., 2017) and for the treatment of patients with unresectable NSCLC that has not progressed after chemoradiation (Antonia et al., 2017). Agonist antibodies targeting immune co-stimulatory receptors are under phase II/III trials (Mayes et al., 2018) and their potential drug-related adverse events will not be specifically covered in the present time.

Agents against CTLA-4 and PD-1 or its ligand PD-L1 may be associated with serious immune-related adverse events (irAE). irAE occur as a consequence of impaired self-tolerance from loss of T-cell inhibition and may potentially hit every organ (i.e., gastrointestinal, skin, endocrine systems). In this review we focused on liver toxicity related to these immunotherapeutic agents for which the largest amount of safety data is available.

2. The irAE panorama

Anti-PD-1 and anti-PD-L1 immune-checkpoint targeted monoclonal antibodies (ICPT mAb) have a comparable toxicity profile (Pillai et al., 2018) and are compressively safer than anti-CTLA4 agents (grade 3 and 4 adverse events in 10–15% versus 20–30%) as well as ICPT mAb combinations (grade 3 and 4 adverse event rate up to 55%) (Larkin et al., 2015). The most common adverse events observed with these agents concern the gastrointestinal system, skin and endocrine glands as shown in Table 1 (Hodi et al., 2010; Borghaei et al., 2015; Larkin et al., 2015; Eggermont et al., 2015; Robert et al., 2015a; Weber et al., 2015; Robert et al., 2015b; Motzer et al., 2015; Robert et al., 2014; Garon et al., 2015; Kim et al., 2013; Wolchok et al., 2010).

The timing of irAE is similar among dermatologic and gastrointestinal systems, occurring earlier (3–4 weeks and around 6 weeks after therapy initiation respectively) when compared to hepatitis and endocrinopathies (usually after 9 weeks of therapy). Unlike anti-CTLA-4 inhibitors, the incidence of toxicities with ICPT mAb does not appear to be dose-related (Weber et al., 2017).

Diarrhea and or colitis are commonly observed gastrointestinal events and their incidence at any grade is higher in patients treated with ipilimumab and combination of ipilimumab plus nivolumab compared to agents targeting the PD-1/PD-L1 axis. Liver dysfunction *per se* is not a common adverse event, occurring in approximately 7% of patients receiving anti-CTLA-4 antibodies, in less than 6% of patient treated with nivolumab and in 30% of subjects receiving a combination of immunotherapeutic agents (Larkin et al., 2015; Robert et al., 2015a; Weber et al., 2015; Robert et al., 2015b; Kleiner and Berman, 2012). Severe (G3-G4) gastrointestinal events occurrence is comparable (1–3%) for both ipilimumab and anti-PD-1/PD-L1 agents. Rash and/or pruritus are the most frequent skin irAEs and are more commonly observed in patients treated with ipilimumab, in monotherapy or combined with other ICPT mAb. Rash typically appears as erythematosus, reticular and maculopapular lesions, localized at limbs and trunk. Toxic effects as bullous pemphigoid and Sweet syndrome are rare.

Hypophysitis and alterations of thyroid function, being hypothyroidism more common than hyperthyroidism, are the most frequent endocrinopathies occurring in patient treated with immunotherapeutic agents, in particular among ipilimumab-containing strategies. Hypophysitis is characterized by the presence of fatigue, headache, hypogonadism, hypotension, and hypoglycemia with particular radiographic findings (Spain et al., 2016). Laboratory exams show a low adrenocorticotropic and thyrotropin hormone lavels. Less commonly, luteinizing hormone, follicle-stimulating hormone, growth hormone, and prolactin levels are also found

Drug-related, immune-mediated hepatitis is often asymptomatic. However, in a small number of cases can lead to fulminant hepatitis, rapid liver failure and ultimately to death (Suzuki et al., 2011). A dose-

Table 1
Hepatic adverse events (AEs) observed on clinical trials using ICPT mAbs among diverse tumor populations; NSCL: non-small-cell lung cancer; TPS: tumor proportion score; NR: not reported; HNSCC: head and neck squamous cell carcinoma.

Trial	Primary condition (*n*)	All grades hepatic AEs (%)	Grade ≥3 hepatic AEs (%)
Ipilimumab			
Hodi et al. (2010)	First line unresectable stage III or IV melanoma (511)	13 (5.9)	4 (1.1)
(Larkin et al. (2015))	First line unresectable stage III or IV melanoma (311)	23 (7.4)	7 (2.2)
Eggermont et al. (2015)	High-risk stage III melanoma after complete resection (471)	180 (38)	45 (10)
Robert et al. (2015a)	Unresectable stage III or IV melanoma ≤1 previous systemic therapy (256)	3 (1.2)	1 (0.4)
Pembrolizumab			
Robert et al. (2015a)	Unresectable stage III or IV melanoma ≤1 previous systemic therapy (256)	8 (2.9)	8 (2.9)
Lopes et al. (2018)	First line advanced/metastatic NSCLC, with no sensitizing EGFR mutations or ALK translocations, with PD-L1 TPS ≥ 1% (636)	NR (1.4)	NR (1.1)
Reck et al. (2016)	First line stage IV NSCLC, with no sensitizing EGFR mutations or ALK translocations, with PD-L1 TPS ≥ 50% (		
Le DT and Wang (2015)	Progressive metastatic carcinoma with or without mismatch-repair deficiency (57)	3 (7)	2 (5)
(Seiwert et al. (2016))	Unresectable or metastatic HNSCC, with PD-L1 expression ≥1%	4 (6)	4 (6)
Nivolumab			
Borghaei et al. (2015)	Stage IIIb/IV or recurrent NSCLC after radiation therapy or surgical resection or progression after one prior platinum-based chemotherapy (287)	16 (6)	1 (< 1)
Larkin et al. (2015)	First line unresectable stage III or IV melanoma (313)	24 (7.6)	7 (2.3)
Weber et al. (2015)	Unresectable stage IIIc or IV metastatic melanoma; BRAF wild type progressing to anti-CTLA-4 or BRAFV600 mutated progressing to anti-CTLA-4 and a BRAF inhibitor (268)	18 (6.7)	3 (1.1)
Robert et al. (2015b)	First line unresectable stage III or IV melanoma without a BRAF mutation (206)	2 (1)	1 (0.5)
Motzer et al. (2015)	Advanced or metastatic renal-cell carcinoma with a clear-cell component who had received one or two previous regimens of antiangiogenic therapy	NR	NR
Ipilimumab + Nivolumab			
Larkin et al. (2015)	First line unresectable stage III or IV melanoma (313)	103 (32.9)	45 (14.4)
Durvalumab			
Powles et al. (2017)	Locally advanced or metastatic urothelial cancer whose disease had progressed on, were ineligible for, or refused prior chemotherapy (191)	18 (9.3)	7 (4.6)
Antonia et al. (2017)	Stage III, locally advanced, unresectable NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy (475)	NR	NR
Atezolizumab			
Rittmeyer et al. (2017)	Stage IIIb or IV NSCLC who received one to two previous cytotoxic chemotherapy regimen, at least one platinum-containing regimen (609)	NR	2 (< 1)

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