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Review article

Immune checkpoints aberrations and gastric cancer; assessment of prognostic value and evaluation of therapeutic potentials

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Contents

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ABSTRACT

Till now, the prognosis of advanced gastric cancer looked dreadful; thus the search for newer better approaches for this lethal disease has been a strategic target for cancer researchers. In recent years, important immunobiological aspects of the tumor have been revealed with the subsequent proposal of immune check point inhibitors to target these pathways. Clinically, unselected use of immune checkpoint inhibitors in gastric cancer has been deemed with failure; in contrast to the clear success of more recent studies reporting on the use of pembrolizumab in molecularly selected patients. This may illustrate that any future use of immune checkpoint inhibitors in gastric cancer has to be molecularly supported. This review provides a delicate dissection of the clinical and immunobiological considerations underlying the use of these agents in addition to a thorough review of the published clinical data of immune checkpoint inhibitors in gastric cancer.

1. Introduction

Gastric cancer (GC) is an important cause for mortality and morbidity; it lies in the 4th rank as an etiology of cancer-related death in males and in the 5th rank of cancer-related death in women

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Table 1
Clinical experience with immune checkpoint inhibitors in advanced gastric cancer.

Study	Number of patients	Agent used	ORR	PFS	OS	Grade 3–4 toxicities
Ralph et al.	18 patients	Tremelimumab	6%	N/R	N/R	*Dizziness, diarrhea and rash. *single death due to bowel perforation that complicated colitis.
Muro et al.	39 patients	Pembrolizumab	32% in Asian pacific patients and 30% in rest of the world	N/R	N/R	*Hypoxia, peripheral neuropathy, and pneumonitis

(Jemal et al., 2011). A marked geographical/ethnic variation has been observed for gastric cancer with about 70% of cases reported in Eastern Europe, South America, and Asia (Parkin et al., 2005). This has been attributed to differences in environmental factors (e.g. H. pylori infection), lifestyle/dietary factors in addition to genetic factors (Fitzgerald et al., 2010; Abdel-Rahman, 2015a).

Till now, the prognosis of advanced gastric cancer looked dreadful; thus the search for newer better approaches for this lethal disease has been a strategic target for cancer researchers (Kordes et al., 2014). The most commonly studied alternative therapies have focused on targeting novel molecular pathways like EGFR, VEGF, c-MET, IGF and more recently immune checkpoints (Abdel-Rahman, 2014a,b, 2015b). In recent years, important immunobiological aspects of gastric cancer have been revealed with the subsequent proposal of immune check point inhibitors to target these pathways. However, what seems missing among this plethora of old and new therapeutic options is the availability of reliable prognostic and predictive biomarkers that can help establish personalized therapy algorithms for these patients.

This review evaluates the basic and clinical aspects underlying the use of immune checkpoint inhibitors in gastric cancer with particular focus on the methods to optimize the outcome with these agents Table1.

2. Basic biology of immune checkpoints

T lymphocytes have an important role in orchestrating the immune system. However, this power of T lymphocytes to combat invading organisms/malignant cells must be controlled by checkpoints that prevent targeting of normal self tissues (Intlekofer and Thompson, 2013). Selective inhibition of these natural inhibitory mechanisms/checkpoints may thus lead to activation of T lymphocytes and thus promote stronger anti-tumor responses (Topalian et al., 2012). Among immune inhibitory receptors, CTLA-4 and PD-1 are the two receptors for which blocking agents have been well developed and validated clinically as anti cancer strategies (Fig. 1) (Robert et al., 2011a).

2.1. CTLA-4

CTLA 4 was initially recognized as an inhibitory receptor expressed on the surface of activated T lymphocytes. In resting T cells, CTLA-4 protein cycles from the Golgi apparatus to the cell surface, and this is followed then by rapid endocytosis (Alegre et al., 1996). CTLA 4 exerts its inhibitory effect through competitive inhibition with the inhibitory receptor CD28 on the surface of T cells (as both receptors share the same ligands; B 7–1 and B 7–2) (Insley et al., 1991). Another inhibitory mechanism of CTLA 4 seems to be mediated by its cytoplasmic portion which interacts with a number of signaling molecules that inhibit proximal signaling via the stimulatory receptor CD28 (Miyatake et al., 1998). Soon after the discovery of the inhibitory potential of CTLA-4, a number of preclinical mouse models have investigated the effects of its blockade. These models illustrated clearly that CTLA-4 blockade enhances the rejection of transplanted tumors as well as fosters the rejection of established tumors (Leach et al., 1996; Peggs et al., 2008).

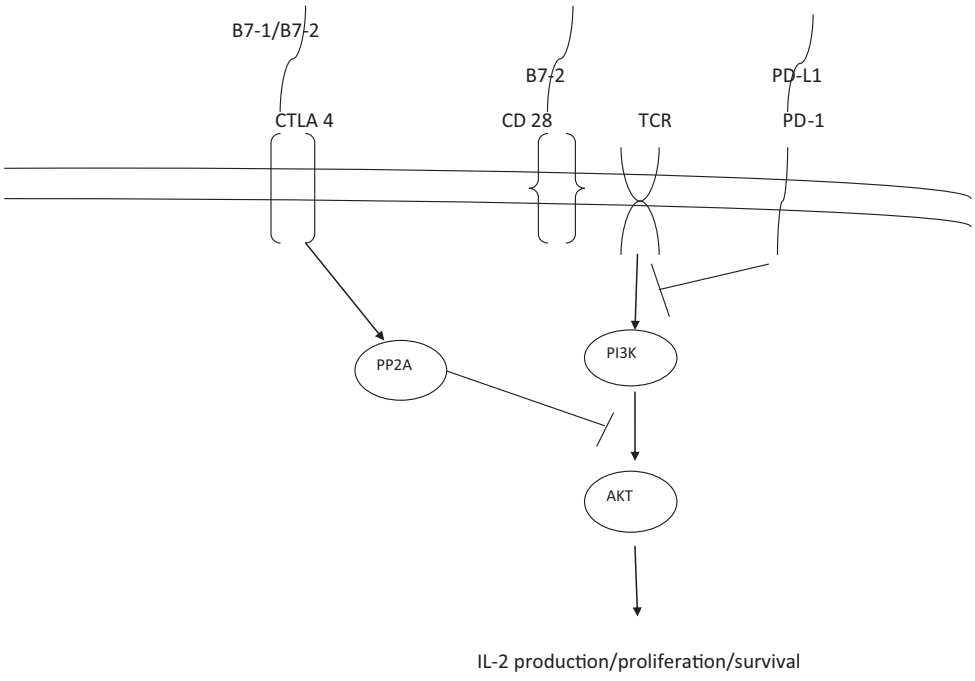

Fig. 1. Intracellular signaling mechanisms by CTLA 4 and PD-1. TCR: T cell receptor.