Cancer Immunotherapy-related adverse events: causes and challenges

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Running title: Adverse effects of cancer immunotherapy

Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; sections on immunological mechanisms were shared equally by AGB and RA, while BLR and DBJ provided clinical input and oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

Acknowledgments

Professor BL Rapoport is supported by supported by the Cancer Association of South Africa (CANSA) and the National Research Foundation (NRF) of South Africa.

Dr. I. Glezerman is supported by the NIH/NCI (Cancer Center Support Grant P30 CA008748)

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Abstract

Despite the success and ongoing promise of monoclonal antibody-targeted immune checkpoint inhibitor immunotherapy of advanced malignancies, in particular, antibodies directed against CTLA-4 and PD-1/PD-L1, the development of immune-related adverse events (irAEs) remains a constraint of this type of therapy. Although rarely fatal, the occurrence of irAEs may necessitate discontinuation of immunotherapy, as well as administration of corticosteroids or other immunosuppressive therapies that may not only compromise efficacy, but also predispose for development of opportunistic infection. Clearly, retention of efficacy of immune checkpoint-targeted therapies in with concurrent attenuation of immune-mediated toxicity represents a formidable challenge. In this context, the current brief review examines mechanistic relationships between these events, as well as recent insights into immunopathogenesis, and strategies which may contribute to resolving this issue. These sections are preceded by brief overviews of the discovery and functions of CTLA-4 and PD-1, as well as the chronology of the development of immunotherapeutic monoclonal antibodies which target these immune checkpoint inhibitors.

Keywords: Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) • Ipilimumab • Microbiome • Nivolumab • Programmed cell death protein 1 (PD-1) • Regulatory T lymphocytes (Tregs)

Introduction

The relatively recent renaissance of cancer immunotherapy undoubtedly represents the most significant development in the treatment of malignant disease to have occurred during the past several decades. This has resulted from major advances and innovations in immunological and biomolecular technologies. These, in turn, have led to the unravelling of various mechanisms of immune regulation, many of which can be exploited by tumors, enabling their growth and spread. With respect to impact on the immunotherapy of cancer, the discovery of two members of a family of immunoregulatory proteins, known as immune checkpoint inhibitors (ICIs), represents the most significant development to date. These proteins, known as CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein-1) and its ligands, PD-L1 and PD-L2, discovered in the early-to-mid-1990s, are recognized as being intimately involved in suppressing anti-tumor immune responses [1, 2].

CTLA-4

In 1987, the co-inhibitory receptor, CTLA-4, was cloned [3]. This molecule is a protein, which competes with the co-stimulatory signaling molecule, CD28, expressed on effector T cells for the activation ligands, CD80/CD86 (also known as B7.1/B7.2), expressed on antigen presenting cells (APCs, predominantly dendritic cells, as well as macrophages). Importantly, the binding affinity of CTLA-4 for CD80/CD86 is approximately 100 times higher than that of CD28, effectively suppressing antigen-activated T cell receptor (TCR) signaling, preventing T cell activation [4]. During the course of an immune response, activated T cells express increasing levels of CTLA-4 as a result of sustained activation due to constant antigen exposure. This scenario is normal in chronic infections and cancer to prevent over-reactivity of immune responses [5]. In this context, the crucial role of CTLA-4 in immune regulation has been convincingly demonstrated in gene knockout mice, in which ablation of CTLA-4 resulted in the development of a lethal lymphoproliferative disorder [6].

In adddition to effector CD4 and CD8 T cells, which express CTLA-4 following antigen stimulation, another T cell population, known as regulatory T cells (Tregs) constitutively (spontaneously) express high levels of CTLA-4, enabling these cells to effectively suppress immune responses [7]. Although Tregs are particularly important in preventing the development of autoimmune and autoinflammatory disorders, over-

activity of these cells poses the risk of development of cancer and infection. In the setting of cancer, blockade of CTLA-4 enhances anti-tumor immunity not only by releasing the brakes on anti-tumor effector T cells, but perhaps more importantly, by attenuating the potent regulatory functions of Tregs [8].

Following promising results in pre-clinical and clinical trials, originating from the pioneering work of Dr. James Allison´s team at the MD Anderson Cancer Center, the Food and Drug Administration (FDA) of the United States approved the therapeutic application of neutralizing monoclonal antibodies (mAbs) against CTLA-4 for metastatic melanoma in 2011. Although this type of immunotherapy proved successful in only 20-30% of patients, most of these showed long- term positive responses, previously unthinkable for advanced melanoma.

PD-1/PD-L1

Subsequently, the PD-1/PD-L1/PD-L2 axis became the most studied immune checkpoint system in the onco-immunology field. The PD-1 receptor was discovered by Dr. Tasuku Honjo in the 1990s [2]. As the name implies, PD-1 plays a crucial role in promoting programmed death of lymphocytes. However, only after the successful genetic engineering of PD-1 gene knockout murine models, which resulted in the development of a lupus-like syndrome, was the involvement of PD-1 in immune regulation revealed [9]. Later, in collaboration with Dr. Honjo´s research team, Dr. Arlene Sharpe and Dr. Gordon Freeman discovered that the PD-1 ligands, PD-L1 and PD-L2, were expressed on tumor cells, corroborating the role of the PD-1/PD-L1/PD-L2 axis in suppressing anti-tumor immunity [10].

Like CTLA-4, PD-1 is expressed on Tregs, as well as on effector T cells, following sustained, antigen-driven T cell activation, as an additional mechanism to control the reactivity of these cells. This immunosuppressive mechanism was first described in the setting of chronic viral infections and later in cancer [11]. Importantly, the PD-1 ligand, PD-L1, is expressed on APCs, cancer cells and endothelial cells, while PD-L2 is mainly restricted to APCs, although it may also be expressed on tumor cells. Contact between PD-1 and its ligands activates signals which suppress T cell priming and proliferation [12]. In this context, blockade of PD-1/PD-L1 enhances anti-tumor immunity by reactivating dysfunctional CD4 and CD8 tumor-specific T cells [13].

Although the development of CTLA-4-targeted strategies triggered the revival in anti-cancer immunotherapy, monoclonal antibody-based blockade of PD-1 has become

the most prominent type of immunotherapeutic anti-cancer modality, administered either alone, or in combination with other therapeutic strategies. In 2014, mAb-based PD-1 blockade was approved for the treatment of advanced melanoma. One year later, as a result of convincing clinical trial data, PD-1 targeted monoclonal antibody-based therapy was approved for non-small cell lung cancer and renal cell carcinoma. Later, in 2016, head and neck cancer and Hodgkin's lymphoma were added to the list of approvals, while in 2017, the list was extended to include urothelial carcinoma and all solid tumors with DNA repair machinery deficiencies. In the case of PD-L1-neutralizing monoclonal antibodies, these were approved for the treatment of urothelial and bladder cancer as well as some forms of lung tumors in 2016 [14].

Immunotherapeutic targeting of CTLA-4 and PD-1/PD-L1

Predictably, and as mentioned in the preceding sections of this review, recognition of the key involvement of CTLA-4 and PD-1 (as well as its ligands, PD-L1 in particular, and PD-L2) triggered the pursuit of safe and effective strategies to counter the immunosuppressive activities of these checkpoints in the setting of treatment of advanced malignant disease. This ambition has been realized through innovations in mAb technology, which have enabled the design and production of MAbs, such as ipilimumab and nivolumab/pembrolizumab, both fully human mAbs , of the immunoglobulin G1 (IgG1) and IgG4 isotypes, which target CTLA-4 and PD-1, respectively [15]. Now widely used in the treatment of different types of metastatic disease, the clinical application of these ICI-targeted mAbs does, however, necessitate close monitoring of patients due to the potential for development of a spectrum of side-effects known as immune-related adverse events (irAEs) [16, 17]. As described extensively in the accompanying articles in this issue of the "Journal", irAEs affect all major organs and may present as newly-diagnosed disorders, or less commonly as exacerbations of pre-existing autoimmune/auto-inflammatory diseases. The development of irAEs associated with ICI-targeted immunotherapy results from attenuation of CTLA-4-/PD-1-mediated immunoregulatory constraints, leading to a broadly over-reactive immune system. The immunopathogenesis and prevention of irAEs represents the remaining focus of this brief review.

Mechanisms underpinning the development of immunotherapy-related IrAEs

Administration of ICI-targeted mAbs results in the reactivation of dysfunctional adaptive and innate immunity, which may encompass beneficial therapeutic effects on the anti-tumor response. On the downside, however, over-reactivity of the immune system also predisposes for development of irAEs.

This contention is supported by a spate of recent publications highlighting the strong correlation between the anti-cancer therapeutic efficacy of ICI-mediated immunotherapy and the frequency and severity of irAEs [reviewed in 18].

Mechanisms underpinning the immunpathogenesis of irAEs are likely to be multifaceted, encompassing hyperactivation of B cells and augmentation of autoantibody production in diseases such as myasthenia gravis, autoimmune hemolytic anemia and type 1 diabetes mellitus, while others such as rheumatoid arthritis, colitis and multiple sclerosis are predominantly T cell-driven disorders.

Intriguingly, although incompletely understood, an increasing number of studies, both pre-clinical and clinical, has linked alterations in immune homeostasis in the gastrointestinal tract (GIT), which accommodates large numbers of Tregs [19], to both the clinical efficacy and immune-mediated toxicities of ICI-targeted MAbs [20].

In this context, broad expansion of gut-associated, pro-inflammatory $CD4^+$ Th17 cells, with both anti-tumor and autoimmune/autoinflammatory potential represents a potential mechanism of ICI therapy-associated irAEs [21]. Indeed, the recent identification of the involvement of commensal bacteria of the gut microbiome as prominent determinants of the anti-cancer efficacy of ICI-targeted mAbs is in keeping with the role of the gut-associated immune system in driving anti-tumor immunity, as well as the pathogenesis of some types of irAEs [22, 23]; moreover, different species of bacteria have recently been correlated with responses to anti-CTLA-4 and anti-PD-1 therapies [24]. Potential, albeit unproven, mechanisms underpinning this relationship include the following:

- attenuation of immune constraints imposed by Tregs results in immune recognition of gut commensal organisms, thereby priming dendritic cells for antigen presentation and activation of $CD4^+$ and CD8+ effector cells reactive with commensal-derived antigens that are cross-reactive with tumor antigens and/or autoantigens [25];

- notwithstanding diminished reactivity of Tregs, certain types of gut commensal bacteria appear to be critically involved in the priming of a subset of intestinal dendritic cells necessary for activation and expansion of Th17 cells, which have the potential to migrate to distant anatomical sites [26].

Irrespective of which of these, or any other mechanisms, are operative in the setting of ICI mAb-mediated anti-cancer immunotherapy, disentangling therapeutic activity from development of irAEs clearly represents a very challenging prospect, which may necessitate manipulation of the gut microbiome [26-28], a strategy that is being studied in a myriad of clinical trials [24]. Additional, albeit largely unexplored approaches, include attenuation of the pro-inflammatory activities of Th17 cells. This may be achieved by administration of monoclonal antibodies that target cytokines which drive expansion of Th17 cells, specifically interleukin(IL)-1β, IL-6, IL-23, as well as those that directly target IL-17 or its receptor [18, 29]. Alternatively, strategies which increase the therapeutic efficacy of ICI-based immunotherapy may also enable shortening of the duration of treatment, which, in turn, may attenuate the development of irAEs. Such strategies include identification of biomarkers of treatment efficacy, as well as those which augment the anti-tumor efficacy of ICI-targeted mAbs.

Identification of biomarkers predictive of treatment efficacy and posible reduced risk of development of IrAEs

During the last two years, analysis of the tumor mutational burden (TMB) has gained prominence, largely due to the findings of several clinical trials which reported good correlations between high TMB and response to ICI-based therapy [30–32]. In this context, a high tumor mutational burden translates into broader tumor antigenicity, resulting in a more intense infiltration of immune cells to the tumor site. On the other hand, it has been reported that broadening of tumor antigen heterogeneity compromises the efficacy of host anti-tumor immune defenses [33, 34], possibly because the expression of fewer, more evenly distributed, tumor antigens elicits a more robust and effective immune response. Clearly, additional research is necessary to accurately establish the relevance of the TMB as a biomarker of the efficacy of ICI-based immunotherapy.

Pre-treatment detection of PD-L1 expression on tumor cells represents an alternative

strategy to predict the potential efficacy of PD-1-based immunotherapy. In this context, expression of PD-L1, even at low levels, on non-small cell lung carcinomas is considered to be a useful predictor of responsiveness to PD-1-targeted monotherapy. In addition, simultaneous expression of PD-L1 on both tumor and infiltrating immune cells in triple-negative breast and bladder cancers may also be predictive of the efficacy of PD-1-based immunotherapy [35–37]. However, the correlation between PD-L1 expression and response is imperfect within these tumor types, as well as in other cancers (including renal cell carcinoma), indicating that measurement of PD-L1 has minimal/no predictive capacity in these settings.

Potentiation of ICI-targeted anti- tumour-immune responses

Resistance mechanisms which impair the efficacy of anti-tumor immunotherapy include: i) impaired T cell migration and infiltration through tumor parenchyma; ii) low-level presentation of tumor antigens; and iii) increased recruitment of immunosuppressive cell populations and tumor-derived immunosuppressive factors [38]. To counter these obstacles to successful immunotherapy, personalized screening tests are being developed to determine which of these mechanisms are operative in individual patients. This, in turn, may enable detection of the best combination of immunotherapies to improve response rates and overall survival. These include: i) strategies to attenuate the influx and/or activities of immunosuppressive cell types, including Tregs in particular, as well as myeloid-derived suppressor cells (MDSCs) and M2-type macrophages; ii) CAR (chimeric antigen receptor) T cell therapies; iii) cytokine-based therapies; and iv) combinations of different types of ICI-targeted mAbs [39].

Another potential, possibly more practical and less expensive strategy, is to combine ICI-based immunotherapy with inducers of immunogenic cell death, specifically radiotherapy, targeted therapy and selected chemotherapeutic agents such as anthracyclines [18]. These agents potentiate localized anti-tumor immune responses via the release of damage-associated molecular patterns (DAMPS) from dead and dying tumor cells, a process known as immungenic cell death, which may harmonize with ICI-based imunotherapy by stimulating the innate immune response [40].

These various potential strategies to ameliorate the development of irAEs in the setting of retention of efficacy of ICI-based immunotherapy are summarized in Table 1.

Table 1: Potential strategies to ameliorate the development of immune-related adverse events during checkpoint inhibitor-based immunotherapy in the setting of retention of therapeutic efficacy

Strategy	Potential benefit
Manipulation of the gut microbiome with biopharmaceuticals	Re-direction of gut-associated immune responses to a more favorable, selective tumor-directed phenotype
Cytokine targeting of Th17 cells	Attenuation of the pro-inflammatory activities of Th17 cells
Identification of biomarkers predictive of treatment efficacy	Shorter duration of immunotherapy and possible lesser probability of development of irAEs
Combination therapy with other immunotherapeutic agents, or with inducers of immunogenic cell death	Shorter duration of immunotherapy due to potentiation of anti-tumor host defenses and lesser probability of development of irAEs

Conclusions

ICI-based immunotherapy of cancer, either as monotherapy, or as an adjunct to radiation therapy, chemotherapy and/or surgery will undoubtedly become a future cornerstone of oncology. Refinements to current immunotherapeutic strategies, however, remain a priority, specifically with respect to improved theraputic efficacy in the setting of attenuation of irAEs. Although useful in controlling irAEs, conventional immunsuppressive agents such as corticosteroids in particular, as well as tumor necrosis factor-α-targeted mAbs (infliximab, adalimumab, golimumab, certolizumab) are certainly not ideal, as these agents may not only counter the efficacy of ICI-based therapy, but also pose the risk of development of opportunistic infections. Future, more promising strategies to ameliorate the risk of development of irAEs in the setting of retention of, or even improved, therapeutic efficacy, include beneficial manipulation of the gut microbiome with biopharmaceuticals, as well as attenuation of the pro-inflammatory activities of Th17 cells via mAb-mediated targeting of the cytokine (ixekizumab, secukinumab) or its receptor.(brodalumab) Strategies which may enable augmentation of ICI-based anti-tumor immunity, possibly enabling decreased duration of immunotherapy, include pre-therapy identification of biomarkers of favorable clinical responses, as well as combinations of ICI-targeted mAbs with other types of immunotherapy and/or inducers of immunogenic cell death.

Conflict of interest

AB, RA, JC, TC, PG, DG and VRS have no conflict of interest to declare. MC reports grants from Novartis, other from Neoleukin Therapeutics, personal fees from Partner

Therapeutics, personal fees from Tillotts Pharma, grants from Genentech, outside the submitted work. MG reports other from Bristol Myers Squibb (BMS), other from AstraZeneca, outside the submitted work. IG reports other from Pfizer Inc, personal fees from CytomX Inc, outside the submitted work. DBJ reports other from Array Biopharma, grants and other from BMS, grants from Incyte, other from Jansen, other from Merck, other from Novartis, outside the submitted work; In addition, DBJ has a patent Co-inventor on use of CTLA-4 agonist for IAEs pending. BLR reports personal fees and other from Merck and Co, grants, personal fees and other from BMS, grants, personal fees and other from Roche South Africa, personal fees and other from AstraZeneca, during the conduct of the study. MSA reports personal fees from Gilead, grants from Pfizer, personal fees from Abbvie, outside the submitted work; All work with these entities has ended.

Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; sections on immunological mechanisms were shared equally by AGB and RA, while BLR provided clinical input and oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

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