

Immunotherapy in Cancer: Incremental Gain or a Quantum Leap?

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ARTICLE INFO

Article history:

Received: 4 December 2016

Accepted: 4 December 2016

Online:

DOI 10.5001/omj.2017.01

Over the past two decades, there has been a considerable improvement in survival of patients with cancer. Prevention, screening and early detection, and treatment, have been credited with the reduction in mortality.¹ The last two years have seen an overwhelming amount of publications on the use of immune checkpoint inhibitors for the management of various cancers. The claims are astounding. Difficult-to-treat cancers respond to the treatment, and patients live longer with good quality of life. Given the excitement, the all-important question to ask is whether ‘immunotherapy’ will prove to be another incremental gain, frequently observed in cancer practice over the past half-century, or is it going to be one of the few quantum leaps, rarely observed in clinical practice?

Ever since the advent of cytotoxic chemotherapy, quantum leaps can be counted on fingers. Combination chemotherapy with MOPP helped cure more than 60% of patients with Hodgkin lymphoma (HL).² The discovery of cisplatin revolutionized the management of germ cell tumors of the testis and subsequently many other cancers.³ The benefit of the adjuvant chemotherapy and hormone was shown by the Early Breast Cancer Trialists’ Collaborative group,^{4,5} and then adjuvant treatment became the standard of care for many cancers. With the turn of the century, targeted therapy in the form of imatinib, trastuzumab, and rituximab changed the face of treatment of chronic myeloid leukemia,⁶ HER-2 expressing breast cancer,⁷ and B-cell non-Hodgkin Lymphoma (B-NHL).⁸ New generation of cytotoxic compounds, substitution of toxic compounds with less toxic substitutes, maintenance regimens in selected cancers, addition of biological agents, such as anti-angiogenic therapy, more sophisticated

targeted therapy, and supportive care — all led to significant but relatively modest improvements in the outcomes of various types of cancer.

Immunotherapy, as a form of cancer treatment had been knocking the door since 1957, when antigenicity of tumors and immune surveillance in tumorigenesis was first recognized.⁹ Interferon and interleukin-2 (IL-2) are used as immunomodulating agents, with modest success for cancers like malignant melanoma. However, it was only in the last five years when the potential for two different types of agents came to fore.^{10,11} Monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4 antibody), and program death receptor (anti-PD-1 and its ligand anti-PD-L1 antibody) have produced astonishing responses in various tumor types.^{12,13} The mode of action of these compounds is predicated in the tumors escaping immune surveillance due to upregulation of negative costimulatory receptors CTLA-4 and PD-1. The anti-CTLA-4 antibody turns off the inhibitory mechanism interrupting the destruction by T-lymphocytes, whereas the anti-PD-1 antibody acts by blocking a negative regulator of T-cell activation (PD-L1), thus allowing the immune system to attack the tumor.

The response rates, especially in difficult-to-treat cancer are unprecedented. For example, the response rate to the anti-CTLA-4 antibody in metastatic melanoma is almost 20%, to anti-PD-1 antibody is 45%, and to the combination is 55%.¹⁴ This is compared to a modest 10–15% seen with combination chemotherapy or IL-2. Similarly, response rates in non-small cell lung cancer (NSCLC), including squamous cell cancer, squamous cell cancers of the head and neck, clear cell carcinoma of the kidney, and previously heavily pretreated cases of HL with the immune

checkpoint inhibitors are unparalleled.¹⁵ Not only responses occur more frequently, they are also more rapid, deeper, and durable. The survival gains are also impressive. Both progression free and overall survivals have been reported in trials related to stage IV malignant melanoma, NSCLC, and relapsed metastatic clear cell carcinoma of the kidney.¹²⁻¹⁴

The side effects of immune checkpoint inhibitors are also different from the side effects of cytotoxic chemotherapy. Side effects are immune related, and are managed with standard treatment.¹⁶ Fortunately, the life-threatening side effects are not common. In addition to the efficacy, the favorable risk-benefit profile and better quality of life further supports the use of immune checkpoint inhibitors in the management of these cancers.

Like many other targeted therapies, it is plausible that immune checkpoint inhibitors would be more effective if the target were identified. Several studies tried to determine if the efficacy of anti-PD-1 inhibitors correlated with PD-L1 ligand expression in tumors.¹⁷ Whereas, malignant melanoma and relapsed HL respond regardless of expression of PD-1 receptors, response rates are significantly higher in PD-L1 positive NSCLC.

Due to efficacy and favorable risk-benefit profile, immune checkpoint inhibitors are being regarded as a game-changer in several cancers. Although immune checkpoint inhibitors demonstrate efficacy across multiple tumor types, it is also clear that a subgroup of patients do not respond. Also, toxicity may occur, especially in the form of less-described 'financial toxicity'. What remains to be seen is whether this form of treatment would produce another small incremental gain, or would prove to be a quantum leap in the war against cancer.

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