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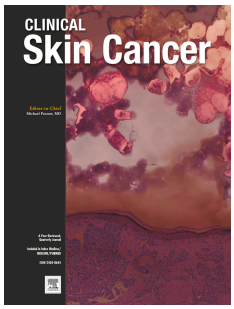

Immunosuppressive agents and their role in managing immunotherapy toxicities in melanoma

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Immunosuppressive agents and their role in managing immunotherapy toxicities in melanoma

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Abstract

Immune checkpoint inhibitors (IO) have changed the landscape of treatment of advanced cancer. Substantial and durable responses are achieved for patients who previously had few or no efficacious systemic treatment options available to them. IO are often well tolerated, however uncontrolled and unexpected off target effects can occur, resulting in wide ranging and varied toxicities. This review discusses the current management of organ-specific IO associated toxicity in metastatic melanoma; with a focus on skin toxicity, colitis, endocrinopathies and IO induced kidney injury. Furthermore, we describe the immunology behind IO induced toxicity, propose improvements on current practice and highlight areas in need of further research.

Introduction

Immune-evasion and tumour promoting inflammation are now recognised as emerging hallmarks of cancer.[1] Cancer suppresses and evades host immunosurveillance by a number of mechanisms, including overexpressing immunosuppressive surface ligands, which in turn interact with T cells and inhibit their function.[1,2] Anti-tumour immunity can, in some cases, be restored by immune checkpoint inhibitors (IO); these novel agents overcome the immunosuppressive signals and allow cancer to be recognized by the immune system enabling immune mediated destruction of cancer cells.[1,4,5]

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is an inhibitory checkpoint protein expressed on T cells. Under normal conditions, CTLA-4 binds to B7 and associated proteins expressed on antigen presenting cells and results in inhibition of T cell function and subsequent regulation of the host immune response.[6] Ipilimumab and tremelimumab are anti-CTLA-4 monoclonal antibodies, which bind directly to CTLA-4, thereby preventing interaction with B7 and in turn causes CD28 mediated upregulation of T cell activity with consequent identification and destruction of cancer. Ipilimumab is approved for use in metastatic melanoma.

Program death ligand 1 (PD1) is another inhibitory checkpoint protein expressed on the surface of activated T cells, B cells, natural killer cells and monocytes.[6] Once again, PD1 is key in the prevention of auto-immunity and promotion of self-tolerance. Pembrolizumab and nivolumab are established anti-PD-1 monoclonal antibodies, which are both licensed for use in metastatic melanoma. In melanoma anti-PD1 agents confer a 33.7-44.6% response rate with excellent durable responses seen.[7,8] These anti-PD1 agents are also licensed in renal cell cancer, head and neck cancer, non-small cell lung cancer (NSCLC) and hodgkins lymphoma. Program death ligand 1 (PD-L1) is a member of the inhibitory B7 protein superfamily and is often overexpressed on tumour cells.[9] Avelumab, atezolizumab and durvalumab are anti-PDL-1 monoclonal antibodies, which have proven activity in metastatic bladder cancer, merkel cell cancer and metastatic NSCLC.[10-12]

Combination anti-CTLA-4 and anti-PD-1 therapy has come to the fore. Combined anti-CTLA-4 and anti-PD1 agents significantly improve upon response rates, with 58.9% complete and partial response rates seen when used first line in metastatic melanoma.[8,13] The increased response rate however comes with a significant toxicity cost with 39.6-45% incidence of grade 3-5 events.[8,13]

The advent of immunotherapy is truly life changing for many patients with metastatic cancer. Meaningful durable responses are seen in patients who previously had no or limited systemic