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## High Dose Cyclophosphamide for the Treatment of Severe Immune Checkpoint Inhibitor Related Adverse Events

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### Abstract

**Introduction:** Immune-related adverse events (irAEs) are a group of autoimmune syndromes that arise following therapy with immune checkpoint inhibitors (ICIs) and are characterized by disinhibition of cell-mediated immunity and decreased self-tolerance. First line treatment of irAEs is typically steroids. Severe irAEs that are refractory to steroids can be life threatening and treatment protocols are an area of unmet need. Standardized clinical guidelines for management of severe corticosteroid refractory irAEs are currently not available and thus are an area of unmet need.

**Cases:** We present two patients who were treated with nivolumab and subsequently developed steroid refractory irAEs in the forms of transverse myelitis, arthritis, and peri-engraftment respiratory distress syndrome.

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**Consent for publication:** Patients provided written consent allowing publication of information pertaining to their disease, clinical history, and therapies used.

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**Conclusions:** Treatment with a single high dose of cyclophosphamide resulted in rapid and sustained clinical improvements in two patients experiencing steroid refractory irAEs following ICI therapy. Cyclophosphamide may benefit patients with wide spectrum of irAEs while having a favorable toxicity profile.

### Keywords

Immune Checkpoint Inhibitors; Immune-related Adverse Events; Cyclophosphamide; Cancer Therapy; Immunology of T-Cells; Immunotherapy

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## Introduction

Since first approval by the Food and Drug Administration (FDA) in 2011, immune checkpoint inhibitors have transformed the cancer treatment landscape [10,11]. ICIs allow for anti-tumor T cell mediated cytotoxicity by blocking negative feedback mechanisms mediated by the interaction of programmed cell death-1 (PD-1) and cytotoxic lymphocyte-associated protein 4 (CTLA-4) receptors on T cells and programmed cell death ligand-1 (PD-L1) and B7 proteins on tumor cells or antigen presenting cells [1,2]. ICIs have a usual spectrum of toxicities attributed to disinhibition of T-cells, termed immune-related adverse events [2]. Such ICI adverse events manifest as inflammatory syndromes affecting nearly every organ system [12]. The incidence and severity of irAEs range widely depending on the agents used, doses, duration of treatment, and malignancy being treated. Severe irAEs (common terminology criteria for adverse events (CTCAE) grades 3–4) have been reported in up to 50% of patients and can be life-threatening or debilitating if not treated promptly [2]. Steroids are the first line therapy for irAEs. Those refractory to steroids are treated with other immunosuppressing regimens, although with variable efficacy [15,16].

Herein we describe the successful use of a single high dose of cyclophosphamide for the treatment of two cases of steroid refractory irAEs.

## Case Presentations and Diagnostic Assessments

### Case 1

A woman in her mid-fifties with metastatic cholangiocarcinoma was treated with second line nivolumab. After eight cycles of nivolumab, she presented to the hospital with acute onset of bilateral lower extremity numbness and weakness. MRI of spine with and without contrast revealed an abnormal high signal within the upper thoracic spinal cord extending from C6-7 down through the T4 levels and an additional single contrast enhancing lesion within the left spinal cord gray matter at the T1 level. Clinical presentation and radiographic findings were concerning for transverse myelitis. Further workup with lumbar puncture revealed normal white blood cell (WBC) and red blood cell (RBC) counts, as well as normal protein and glucose levels. On cytology cerebrospinal fluid (CSF) contained a few lymphocytes and but was negative for malignant cells. CSF infectious workup was negative for BK, JC, cytomegalovirus (CMV), herpes simplex (HSV) 1 and 2 viruses by polymerase chain reaction (PCR). Autoimmune workup with antinuclear antibody (ANA), anti-double stranded DNA (dsDNA), rheumatoid factor (RF), SSA/SSB, anti-smooth muscle

antibody, anti-mitochondrial antibody, neuromyelitis optica (NMO) IgG, and anti-AQP4 antibody was negative. Treponema, syphilis, and Lyme antibody tests were also negative. Given that no other inciting triggers were identified, she was diagnosed with ICI-related transverse myelitis. She was initiated on methylprednisolone 1g per day with initial improvement in sensation and strength and was then discharged on dexamethasone 4 mg three times a day. However, two weeks later, she again presented to the hospital with recurrent symptoms, now with left leg numbness and right leg weakness, concerning for worsening transverse myelitis. While admitted, she had 4 sessions of plasma exchange (PLEX) without significant improvement in symptoms. Due to concern for steroid and PLEX refractoriness, she received one dose of cyclophosphamide 1.2 g/m<sup>2</sup>. Within a day of receiving cyclophosphamide, the right leg weakness improved (initial self-reported 80-90% improvement). Neurologic symptoms completely resolved over the next couple of months without additional interventions. She was never retreated with ICIs and instead was placed on maintenance with capecitabine. Over six years later, she remains in a complete remission and has not had recurrence of neurologic irAEs.

## Case 2

A woman in her early twenties with stage II Hodgkin's lymphoma, with disease progression after 6 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), received four cycles of brentuximab vedotin and nivolumab. She developed pain and stiffness in multiple joints which were thought to be ICI-related arthritis. She was treated with prednisone 1 mg/kg daily with good response. She subsequently was consolidated with autologous stem cell transplant (auto-SCT). Upon engraftment she developed fevers, joint pains, and dyspnea which worsened despite anti-microbial treatments and progressed to hypoxemia and circulatory shock requiring intensive care unit (ICU) admission. A CT scan of her chest showed pneumonitis. An extensive workup including bronchoscopy and bronchoalveolar lavage ruled out infectious etiologies. She was diagnosed with peri-engraftment respiratory distress syndrome (PERDS) secondary to ICI. She improved with steroids but then again rapidly deteriorated with another episode of hypoxemia, fevers, joint pains, and circulatory shock despite ongoing treatment with high doses of steroids (prednisone 2 mg/kg daily). She had a very transient improvement after one dose of tocilizumab (8 mg/kg) but continued to have dyspnea, hypotension, tachycardia, and joint pains. Due to her poor response to steroids and tocilizumab and her rapidly deteriorating condition, she was given cyclophosphamide 1 g/m<sup>2</sup> after which her overall clinical condition rapidly improved. To prevent further relapses, she received Intravenous Immunoglobulin (IVIG) and was started on cyclosporine while being tapered off steroids. She tolerated the steroid taper and was also eventually tapered off of cyclosporine. She did have a recurrence of joint pains which responded to weekly low doses of tocilizumab. She is now over six months posttransplant, off all immunosuppression without any symptoms of irAEs. Most recent imaging shows a complete response without evidence of residual Hodgkin's lymphoma.

## Discussion

With increasing use of ICIs, an understanding of mechanisms leading to irAEs is essential for the development of optimal therapies. The pathophysiology of irAEs is multifactorial, involving various components of the immune system. A hallmark for irAEs is the infiltration of healthy tissues by activated effector T cells (T-eff) and reduced self-tolerance due to inhibition of regulatory T cells (T-reg) [3,13]. Activation of CD8<sup>+</sup> T cells can cause cytotoxicity to normal tissues via release of cytotoxic granules (granzymes and perforins) and cytokines (IFN-gamma, TNF-alpha, TNF-beta) [2,4]. Cyclophosphamide is an alkylating agent from the nitrogen mustard family that was developed in the 1940s and remains a mainstay in the treatment of various malignancies. In addition to its anti-neoplastic effects, cyclophosphamide is a potent immunomodulator and has selective T-cell depleting properties with regulatory T cells relatively spared secondary to increased levels of aldehyde dehydrogenase [14]. The latter property has made it one of the most effective agents in the prevention of graft versus host disease (GVHD) after hematopoietic stem cell transplantation (HSCT). Cyclophosphamide is not routinely used for reversal of irAEs. To our knowledge, this is first report of using single high dose cyclophosphamide for steroid refractory irAEs. Pre-clinical work by Strauss et al. showed that when compared to other commonly used immunosuppressive drugs (steroids, calcineurin inhibitors, sirolimus, and mycophenolate mofetil), cyclophosphamide (and methotrexate) depleted autoreactive T cells during thymic selection and eliminated T cells from the periphery. Moreover, cyclophosphamide targets CD95 (member of death receptor family) that is increased on the surface of activated T cells resulting in activation-induced cell death. Thus, cyclophosphamide targets T cells at various stages of development and activation allowing for termination of immune response (Figure 1) [5,6].

The dysregulation of homeostasis between T-eff cells and T-regs by ICI blockade plays an essential role in the development of irAEs [3,13]. Cyclophosphamide's ability to restore the homeostatic balance of T-cell subsets may be another mechanism of how it is able to reverse irAEs. This has been best illustrated in patients who receive anti-PD1 therapy prior to allogeneic HSCT – a group that is known to have an increased risk of severe GVHD. The use of post-transplant cyclophosphamide has been observed to ameliorate this risk, possibly by restoring the homeostatic balance between regulatory and effector T cells [7].

## Conclusion

In this case series we describe two patients with irAEs refractory to first line steroids treated with a single high dose of cyclophosphamide. Both patients had a rapid and sustained response to therapy without any adverse events. Transverse myelitis is a difficult-to-treat irAE with significant residual neurologic deficits present in 5/7 patients reported in the literature [8]. Our patient received combined therapy with steroids, PLEX, and cyclophosphamide and is free of neurologic deficits today, six years later. The second patient suffered from a life-threatening engraftment and respiratory syndrome, which is becoming a rapidly recognized irAE post autologous stem cell transplantation in patients who received prior anti-PD1 therapy [9]. She was refractory to steroids and tocilizumab and

was clinically deteriorating but had a rapid and sustained response to a single high dose of cyclophosphamide.

In conclusion, a single high dose of cyclophosphamide can terminate severe steroid-refractory irAEs. The mechanism is thought to be depletion of cytotoxic T cells and restoration of T-cell homeostasis between effector and regulatory T-cells. Patients with grade 3 and 4 adverse events refractory to first-line steroids may benefit from cyclophosphamide as it may offer a rapid and sustained response.

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### Availability of data and materials:

The original data used in these case reports are protected under HIPPA laws and therefore cannot be disclosed.

### List of Abbreviations

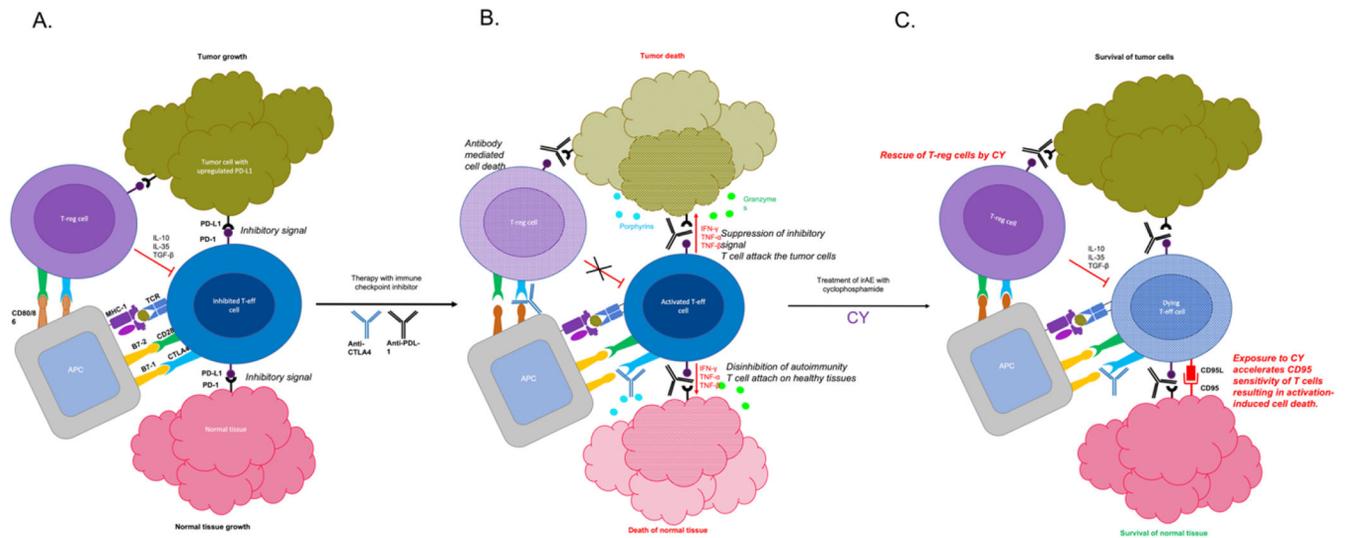
<b>ABVD</b>	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
<b>ANA</b>	Antinuclear Antibody
<b>Auto-SCT</b>	Autologous Stem Cell Transplant
<b>CMV</b>	Cytomegalovirus
<b>CR</b>	Complete Response
<b>CSF</b>	Cerebrospinal Fluid
<b>CTCAE</b>	Common Terminology Criteria for Adverse Events
<b>CTLA-4</b>	cytotoxic lymphocyte-associated protein-4
<b>dsDNA</b>	double stranded DNA
<b>FDA</b>	Food and Drug Administration
<b>GVHD</b>	Graft Versus Host Disease
<b>HSCT</b>	Hematopoietic Stem Cell Transplantation
<b>HSV</b>	Herpes Simplex Virus
<b>ICI</b>	Immune Checkpoint Inhibitors
<b>ICU</b>	Intensive Care Unit
<b>irAEs</b>	Immune-Related Adverse Events
<b>IVIG</b>	Intravenous Immunoglobulin

<b>NMO</b>	Neuromyelitis Optica
<b>PCR</b>	Polymerase Chain Reaction
<b>PD-(L)1</b>	Programmed Cell Death-(ligand)1
<b>PERDS</b>	Peri-Engraftment Respiratory Distress Syndrome
<b>PLEX</b>	Plasma Exchange
<b>RBC</b>	Red Blood Cell
<b>T-eff</b>	Effector T Cell
<b>T-reg</b>	Regulatory T Cell
<b>WBC</b>	White Blood Cell

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**Figure 1:** Mechanism of immune tolerance, immune checkpoint blockade, and proposed effects of cyclophosphamide.

**A.** Antigen presenting cell (APC) transmits inhibitory signals via B7-1/2 interaction with CTLA4/CD28 on T-effector cells (T-eff). Tumor upregulation of PD-L1 transmits inhibitory signals to regulatory T cells (T-reg) that inhibit APCs via CTLA4/CD28 interaction with CD80/86 allowing for increased immune tolerance to tumor antigens. T-reg cells suppress T-eff cells by release of IL-10, IL-35, and TGF- $\beta$ .

**B.** Therapy with immune checkpoint inhibitors (ICIs) results in blockade of inhibitory PD-L1 and CTLA4 signaling resulting in activation of T-eff cells. ICIs also lead to antibody-dependent cell-mediated cytotoxicity of T-reg cells, decreasing self-tolerance and allowing for activated T-eff cells to kill tumor cells via release of IFN- $\gamma$ , TNF- $\gamma$ , TNF- $\beta$ , porphyrins, and granzymes. This also results in attack on healthy tissue resulting in immune related adverse events (irAEs).

**C.** Cyclophosphamide (CY) accelerated CD95 induced T-eff cell death. CY rescues T-reg cells allowing for inhibitory signals to T-eff cells, thus restoring T-cell homeostasis.