Indian Journal of Pathology and Oncology 2022;9(4):392–394

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Letter to Editor

Cytokine release syndrome as a consequence of check point inhibitors nivolimumab and iplimumab

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ARTICLE INFO

Article history:
Received 10-08-2022
Accepted 20-09-2022
Available online 14-12-2022

Immune checkpoint inhibitors like nivolimumab and iplimumab are antibodies to programmed cell death receptor 1 (PD-1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) respectively.[1] They mediate T-cell induced tumor cell destruction by blocking malignant cells' ability to negatively regulate T cell activity, leading to activation of immune and non-immune cells and ultimately a massive release of cytokines.[2,3] In addition to its anti-tumor effect, checkpoint inhibition can lead to loss of maintenance of self-tolerance, leading to immune-mediated adverse events (irAEs).[4]

We report a 46-year-old woman diagnosed with grade IV left renal cell carcinoma with liver and skeletal metastasis, who was started on nivolimumab and iplimumab as third line chemotherapy. Seven days later, she developed a fever of 102°F, hypotension (blood pressure 80/50 mm Hg), hypoxia requiring oxygen of 2l/min to maintain oxygen saturation above 94%, lower limb swelling, haematuria and disorientation. She was resuscitated with fluids and started on broad spectrum antibiotics. Initial laboratory investigations were deranged and are shown in Table 1. Sepsis, tumour lysis syndrome, deep vein thrombosis, disseminated intravascular coagulation and pulmonary embolism were ruled out as well as other immune therapy related complications such as adrenal insufficiency, hypophysitis and hypo-hyperthyroidism pneumonitis. Based on the clinical and laboratory parameters – fever, hypotension, hypoxia, neurologic dysfunction, grade 3 hepatic toxicity (>5 times upper limit of normal/baseline according to common terminology criteria for adverse events (CTCAE) v4.0 grading), coagulopathy and elevated inflammatory markers, a diagnosis of grade 2 CRS was made. She was started on methylprednisolone 1mg/kg/day but succumbed three days later.

It is necessary to identify and treat CRS and other irAEs at the earliest. CRS is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction reported in the setting of chimeric antigen receptor T cell therapy, therapeutic antibodies and haploidentical allogeneic transplantation.[2,5] The timing of CRS symptoms and its severity depends on the agent and the degree of immune cell activation.[4] In one study, out of 58 cases, 43 (74%) reported CRS with anti-programmed death-1/anti-programmed death-ligand 1 agents.[1] The grading of CRS is based on the American Society for Transplant and Cellular Therapy and is divided into 4 grades:[5]

Grade 1 – Fever and constitutional symptoms,

Grade 2 – Fever with hypotension responds to fluids or low dose vasopressors, hypoxia<40% oxygen requirement,

Grade 3 – Symptoms requiring aggressive intervention, oxygen requirement>40%, grade 3 organ toxicity or grade 4

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https://doi.org/10.18231/j.ijpo.2022.096

Table 1: Laboratory investigations

Parameter	Value	Normal range	Parameter	Value	Normal range	Parameter	Value	Normal range
Hemoglobin (gm/dL)	6.7	11.6 – 15	Creatine Phosphokinase (IU/L)	32	10 – 120	Aspartate Transferase (U/L)	307	8 – 33
Total leukocyte count (*103/μL)	38.8	4.0 - 11.0	Lactate dehydrogenase (IU/L)	1361	105 – 333	Alanine Transferase (U/L)	113	4 - 36
Platelets (*103/μL)	257	150 - 450	Ferritin (μg/mL)	4168	11 - 307	Alkaline Phosphatase (IU/L)	924	44 – 147
Sodium (mEq/L)	135	135 – 145	Interleukin 6 (pg/mL)	165	0 – 43.5	Gamma Glutamyl Transferase (U/L)	897	5 – 40
Potassium (mEq/L)	5.71	3.6 – 5.2	Procalcitonin (ng/mL)	21.8	< 0.1	Prothrombin time (seconds)	>130	11 – 13.5
Creatinine (mg/dL)	0.88	0.6 – 1.1	Total bilirubin (mg/dL)	2.18	< 1.2	Partial thrombo-plastin time (seconds)	66.1	25 - 35
Adrenocorticotropic hormone (pg/mL)	74.18	10 - 60	Serum ammonia (μg/dL)	251.23	15 – 45	International normalised ratio	3.2	< 1.1
Serum Cortisol (mcg/dL)	12.87	5 - 25	Serology	Negative	Negative	C-reactive protein (mg/L)	31.10	< 10

transaminitis and

Grade 4 – Life threatening symptoms, grade 4 organ toxicity (excluding transaminitis), ventilator support requirement.

Neurologic irAEs (irAE-Ns) have been reported in a meta-analysis with 3.8%,6.1% and 12% of patients on anti-CTLA-4 inhibitors, anti-PD1 inhibitors, and in combination respectively.[6] Hepatotoxicity has been reported in 10% of patients receiving nivolimumab.[7] CRS needs to be differentiated from mimics like sepsis, tumour progression, tumour lysis syndrome, heart failure, thromboembolism, anaphylaxis and hemophagocytic lymphohistiocytosis.[2]

Mild CRS is treated with antihistamines, antipyretics and intravenous fluids.[5] For Grade 3 and 4 CRS, immune checkpoint inhibitors are discontinued and intravenous glucocorticoids such as dexamethasone 10mg sixth hourly, hydrocortisone 100 mg eighth hourly or methylprednisolone 1mg/kg/day are considered. Tocilizumab is an additional treatment for severe CRS (8 mg/kg body weight for adults and 12 mg/kg body weight for patients < 30 kg body weight). Other treatments n unresponsive patients include anakinra (blockade of IL-1RA), etanercept (blockade of TNF alpha), alemtuzumab, anti-thymocyte globulin, cyclophosphamide, ruxolitinib and ibrutinib.[8]

CRS is a rare but life-threatening complication, and a diagnosis of exclusion, hence, a high index of suspicion is required for diagnosis. Further studies are needed to identify adverse events caused by different immunotherapies, their timing of occurrence and response to various different modalities.

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Cite this article: Shah A, Rangappa P, Jacob I, Rao K, Reddy N. Cytokine release syndrome as a consequence of check point inhibitors nivolimumab and iplimumab. *Indian J Pathol Oncol* 2022;9(4):392-394.