Immunotherapy and Management of Immune-Related Adverse Effects: A Focus on the Immune Checkpoint Inhibitors

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Appendix

Table 1: Immunotherapy Agent Overview[10-15]

Agents	Target	FDA-Approval Date	Dosing	FDA-Approved Indications	Cost[1]
Ipilimumab	CTLA-4	March 2011	3 or 10 mg/kg IV every 3 weeks	Melanoma	240 mg: $42,405 800 mg: $135,696
Pembrolizumab	PD-1	September 2014	200 mg IV every 3 weeks	Melanoma NSCLC Urothelial cancer Hodgkin lymphoma Head & neck cancer Colorectal cancer Gastric cancer	200 mg: $10,994
Nivolumab	PD-1	December 2014	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	Melanoma NSCLC Urothelial cancer Renal cell cancer Hodgkin lymphoma Head & neck cancer Colorectal cancer HCC	240 mg: $7,440 480 mg: $14,880
Atezolizumab	PD-L1	May 2016	1200 mg IV every 3 weeks	NSCLC Urothelial cancer	1200 mg: $10,499
Avelumab	PD-L1	March 2017	10 mg/kg IV every 2 weeks	Urothelial cancer Merkel cell cancer	800 mg: $7,328
Durvalumab	PD-L1	May 2017	10 mg/kg IV every 2 weeks	NSCLC Urothelial cancer	800 mg: $7,181

NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma
[1]Cost based on average wholesale price (AWP); cost for mg/kg dosing based on an 80 kg patient

Table 2: Incidence of Immune-Related Adverse Effects[6-15,20,26-27,32-34]

	CTLA-4 Inhibitors	PD-1 Inhibitors	PD-L1 Inhibitors
Skin Toxicities	37-70%	17-37%	10-26%
Colitis	8-16%	2-3%	2%
Hepatitis	5-11%	2%	≤1%
Endocrine Toxicities	2-7%	1-14%	1-12%
Pneumonitis	<1%	≤5%	≤4%

Table 3: Management of rash/inflammatory dermatitis[6-9]

Grade	CTCAE Criteria	Management	
		ICPi	Immunosuppression
1	Symptoms don't affect quality of life or controlled with topical regimen and/or oral antipruritic	Continue	• Topical emollient and/or mild-moderate potency corticosteroid
2	Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding	• Topical emollient, oral antihistamine, and medium-high potency topical corticosteroid • Consider prednisone (or equivalent) 1 mg/kg[1]
3	Same as grade 2 with failure to respond to indicated interventions	Hold	• Topical emollient, oral antihistamine, and high potency topical corticosteroid • (Methyl)prednisolone (or equivalent) 1-2 mg/kg[1]
4	All severe rashes unmanageable with prior interventions and intolerable	Hold	• (Methyl)prednisolone (or equivalent) 1-2 mg/kg IV with slow taper once toxicity resolves

ICPi: Immune checkpoint inhibitor
[1]Taper over at least 4 weeks

Table 4: Management of colitis[6-9,28-29]

Grade	CTCAE Criteria	Management	
		ICPi	Immunosuppression
1	Increase of fewer than four stools per day over baseline	Continue	None
2	Increase of four to six stools per day over baseline	Hold	• Loperamide if infection ruled out • Prednisone (or equivalent) 1 mg/kg[1]
3	Increase of seven or more stools per day over baseline, incontinence, or hospitalization indicated	Hold[2]	• Prednisone (or equivalent) 1-2 mg/kg[1] • If symptoms persist ≥ 3-5 days or recur, give IV corticosteroids or infliximab 5-10 mg/kg
4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue	• Methylprednisolone (or equivalent) 1-2 mg/kg[1] • If symptoms refractory to corticosteroids within 2-3 days, give infliximab 5-10 mg/kg

Consider giving vedolizumab in patients refractory to infliximab and/or have contraindications to TNF-alpha blocker

[1]Taper over at least 4-6 weeks

[2]CTLA-4 inhibitors should be permanently discontinued; may restart PD-1 and PD-L1 agents if patient recovers to grade 1

Table 5: Management of hepatitis[6-9,30]

Grade	CTCAE Criteria	Management	
		ICPi	Immunosuppression
1	Asymptomatic; AST/ALT > ULN to 3xULN and/or total bilirubin > ULN to 1.5xULN	Continue	None
2	Asymptomatic; AST/ALT 3-5xULN and/or total bilirubin 1.5-3xULN	Hold	• Prednisone (or equivalent) 0.5-1 mg/kg[1]
3	Symptomatic, fibrosis by biopsy, compensated cirrhosis, reactivation or chronic hepatitis; AST/ALT 5-20xULN or total bilirubin 3-10xULN	Permanently discontinue	• Methylprednisolone (or equivalent) 1-2 mg/kg[2] • If no improvement after 3 days, consider mycophenolate mofetil
4	Decompensated liver function (ascites, coagulopathy, encephalopathy); AST/ALT > 20xULN or total bilirubin > 10xULN	Permanently discontinue	• Methylprednisolone (or equivalent) 2 mg/kg[2] • If no improvement after 3 days, consider mycophenolate mofetil

[1]Taper over at least 1 month

[2]Taper can be attempted around 4-6 weeks; optimal duration is currently unknown

Table 6: Management of endocrine toxicities[6-9]

Grade	CTCAE Criteria	Management
Hypothyroidism		
1	TSH < 10 and asymptomatic	• Continue ICPi
2	Moderate symptoms; TSH persistently > 10	• May hold ICPi until symptoms resolve • Thyroid hormone supplementation
3-4	Severe symptoms	• Hold ICPi until symptoms resolve • Thyroid hormone supplementation
Hyperthyroidism		
1	Asymptomatic or mild symptoms	• Continue ICPi
2	Moderate symptoms	• May hold ICPi until symptoms resolve • Beta-blocker for symptomatic relief
3-4	Severe symptoms	• Hold ICPi until symptoms resolve • Beta-blocker for symptomatic relief • If concern for thyroid storm, prednisone (or equivalent) 1-2 mg/kg[1]
Primary adrenal insufficiency		
1	Asymptomatic or mild symptoms	• May hold ICPi until patient stabilized • Prednisone 5-10 mg daily or hydrocortisone 10-20 mg every morning & 5-10 mg every afternoon • May require fludrocortisone 0.1 mg
2	Moderate symptoms	• May hold ICPi until patient stabilized • Prednisone 20 mg daily or hydrocortisone 20-30 mg every morning & 10-20 mg every afternoon[2]
3-4	Severe symptoms	• Hold ICPi until patient stabilized • Stress dose steroids (hydrocortisone 100 mg or dexamethasone 4 mg)[3]

[1]Taper over 1-2 weeks
[2]Taper over 5-10 days to maintenance doses (grade 1 doses)
[3]Taper over 7-14 days to maintenance doses (grade 1 doses)

Table 7: Management of pneumonitis[6-9]

Grade	CTCAE Criteria	Management	
		ICPi	Immunosuppression
1	Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma	Hold[1]	None
2	Symptomatic, involves more than one lobe of the lung of 25-50% of lung parenchyma	Hold	• Prednisone 1-2 mg/kg[2] • Consider empiric antibiotics
3	Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma	Permanently discontinue	• Empiric antibiotics • Methylprednisolone 1-2 mg/kg IV[2] • If no improvement after 48 hours (*1 of the following*): o Infliximab 5 mg/kg, o Mycophenolate mofetil 1000 mg IV BID o IVIG for 5 days o Cyclophosphamide
4	Life-threatening respiratory compromise, urgent intervention indicated (intubation)		

[1]Resume when radiographic evidence of improvement or resolution
[2]Taper by 5-10 mg/week over 4-6 weeks

Table 8: Immunosuppressants used for management of immune-related adverse effects[31,35,38-40]

Agents	Dosing	Mechanism of Action	Adverse Effects
Prednisone	0.5-2 mg/kg (*varies depending on toxicity*)	Suppresses immune system via reducing activity of lymphatic system	Adrenal suppression Infections Myopathy Psychiatric disturbances Hypertension Hyperglycemia GI disturbances
Mycophenolate mofetil	500-1000 mg PO BID	Inhibits inosine monophosphate dehydrogenase (IMPDH) resulting in decreased proliferation of T and B lymphocytes	Infections Lymphoproliferative disorders Cytopenias GI disturbances
Infliximab	5-10 mg/kg IV at 0, 2, and 6 weeks	Tumor necrosis factor alpha (TNF-α) inhibitor	Hematologic toxicities Hepatotoxicity Infections Hypersensitivity & infusion reactions
Vedolizumab	300 mg IV at 0, 2, and 6 weeks	Alpha4beta7 integrin inhibitor resulting in decreased migration of memory T-lymphocytes	Hypersensitivity Infections
Cyclophosphamide	----	Alkylating agent preventing DNA cross-linking decreasing DNA synthesis	Hematologic toxicities GI disturbances Hemorrhagic cystitis Infections