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Immunotherapy in Special Patient Populations

Topics: Immune Checkpoint Inhibitors in:

- Autoimmune disorders
- Organ transplants
- Chronic viral infections
- Concurrent immunosuppressants
- Organ dysfunction
- Pregnancy
- Brain metastases,
- Pediatric
- Elderly

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ICB in patients with pre-existing autoimmune disease

- Systematic review: 123 patients
- Most had metastatic melanoma.
- Preexisting autoimmune diseases : psoriasis and/or psoriatic arthritis, rheumatoid arthritis, autoimmune thyroid disease, ulcerative colitis, Crohn disease, multiple sclerosis, myasthenia gravis, and sarcoidosis.
- 83.5% received prior treatment for their autoimmune disease
- 46.2% had active autoimmune disease with ongoing symptoms
- 43.6% were receiving concomitant treatment (corticosteroids, synthetic or biologic disease-modifying antirheumatic drugs, or other immunosuppressants) at initiation of CPI therapy.

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Abdel-Wahab, *Ann Intern Med.* 2018;168(2):121-130

ICB in patients with pre-existing autoimmune disease

- 1/2 had exacerbation of prior autoimmune disease
  - Generally the same manifestations as those occurring before CPI therapy.
- > 1/3 experienced de novo irAEs
  - colitis and hypophysitis the most common
- No differences in frequency of AEs in patients with active vs inactive preexisting autoimmune dz
- Fewer AEs in those receiving immunosuppressive therapy at initiation of CPI therapy
- Ipilimumab associated with more de novo irAEs; anti–PD-1/PD-L1 agents had more disease flares
- Most AEs were treated with corticosteroids; 16% required other immunosuppressive tx
- AEs improved in more than half of cases without the need to discontinue CPI therapy.
- Death from a serious adverse event was reported in 2.4% of patients.
  - Suggest that irAEs may be more severe in patients with concomitant autoimmune disease.

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Abdel-Wahab, *Ann Intern Med.* 2018;168(2):121-130

ICB in patients with allogeneic HSCT

- Single dose of ipilimumab (ranging from 0.1 to 3mg/kg) in 29 patients with relapsed hematologic malignancies after allogeneic stem cell transplantation: NO GVHD[1]

- ipilimumab at 3 or 10 mg/kg for 4 doses in 28 patients with relapsed hematologic malignancies after stem cell transplantation. GVHD in 14% and irAEs in 21% (including 1 death) [2]
  - Several durable disease responses
- Case reports of anti-PD-1 in allogeneic HSCT.

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[1]Blood. 2009;113:1581-1588; [2]N Engl J Med. 2016; 375:143-153

Solid Organ transplants

Table 3 Summary of literature results and study cohort results

Variables	Liver transplant (literature)	Renal & heart transplant (literature)	PD-1 inhibitors (literature)	CTLA-4 inhibitors (literature)	PD-1 & CTLA-4 inhibitor (literature)	All literature results	Study cohort (liver transplant)	Overall (all results)
Rate of graft rejection	25% (n=12)	43.8% (n=16)	33.3% (n=15)	25% (n=8)	40% (n=5)	32.1% (n=28)	28.6% (n=7)	31.4% (n=35)
Median time to graft rejection (days)	13 (n=2)	8 (n=5)	13.5 (n=6)	–	8 (n=1)	8 (n=7)	24 (n=2)	19 (n=9)
Response rate	33% (n=10)	55.6% (n=9)	66.7% (n=9)	28.6% (n=7)	33.3% (n=3)	47.4% (n=19)	25% (n=4)	43.4% (n=23)
Median PFS (months)	3.8 (n=10)	8 (n=11)	8 (n=11)	5 (n=7)	8 (n=3)	7 (n=21)	1.8 (n=4)	6 (n=25)
Median time to transplant (years)	6 (n=11)	11 (n=15)	9 (n=14)	8 (n=8)	11 (n=4)	8 (n=26)	3 (n=7)	8 (n=33)

PFS, progression free survival; PD-1, programmed death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4.

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Deleon TT, J Gastrointest Oncol. 2018 Dec;9(6):1054-1062.

Chronic immunosuppression

- “Responses may be less frequent in patients receiving high-dose steroids or other disease-modifying therapies (15%) than in those not requiring these agents (44%)” (Reported in Cancer 2017;123:1904-11)

- Patients with brain metastases requiring chronic streoids may have lower response rate to ICB (Margolin, Lancet Oncol. 2012;13:459-465).

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ICB in HIV + patients

- Retrospective review of immunotherapy-treated patient
- 9 patients with HIV and Kaposi Sarcoma
- Median viral load was 20 copies/mL (range, undetectable to 549,704)
- Median CD4 count was 256 cells/μL (range, 10–603).
- Eight patients received nivolumab and one received pembrolizumab.
- Six patients (67%) achieved partial (*N* = 5) or complete remission (*N* = 1).
- No drug-related grade >2 toxicities occurred.
- In seven patients, CD4 counts increased (*P* = 0.09).
- Tumor mutational burden was low, and PD-L1 immunohistochemistry was negative (three and four assessable patients, respectively).
- Responders included patients with low CD4 counts, high HIV load, and/or visceral disease

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Galanina, Cancer Immunol Res. 2018 Oct;6(10):1129-1135

ICB in “elderly”

- **systematic review and meta-analysis** Nishijima, Cancer Treat Rev. 2016;45:30-37.
- Age cut-off of 65-70 years
  - ICIs improved OS in both younger (HR, 0.75; 95% CI, 0.68-0.82) and older (HR, 0.73; 95% CI, 0.62-0.87) groups.
  - Improvement in PFS was observed in younger (HR, 0.58; 95% CI, 0.40-0.84) and older (HR, 0.77; 95% CI, 0.58-1.01) patients.
  - Subgroup analyses according to ICI and tumor type showed a consistent survival benefit in both younger and older groups
    - Exception: subgroup of older patients treated in 4 trials of anti-programmed cell death protein-1 (PD-1) monoclonal antibody (HR, 0.86; 95% CI, 0.41-1.83).

Note: Flu vaccine is safe to administer (Clin Infect Dis. 2020 Jan 2;70(2):193-199.)

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ICB in pediatrics

- **A phase I/II study of atezolizumab in pediatric and young adult patients with refractory/relapsed solid tumors (iMATRIX-Atezolizumab).**
- Patients aged < 30 years with refractory/relapsed non-central nervous system solid tumors received atezolizumab every 3 weeks until loss of clinical benefit (< 18 years old, 15mg/kg [maximum dose 1200mg]; ≥18 years old, 1200mg)
- PK data and safety profile were similar to that in adults
  - Tox can occur early: even after the first dose
- 2/5 patients with HL with PR; 1 with atypical rhabdoid tumor (RT) had an unconfirmed PR.

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Geoerger, *Journal of Clinical Oncology* 35, no. 15_suppl (May 20 2017); abstract 10524 .

ICB in organ dysfunction

- No specific contraindication to ICB exists for patients with renal, hepatic, or cardiac dysfunction
  - These patients have been largely excluded from clinical trials
- 27 patients with organ dysfunction (Kanz, J Immunother Cancer. 2016 Oct 18;4:60)
  - Organ dysfunction was defined as cardiac (left ventricular ejection fraction ≤45 %), renal (creatinine ≥2 mg/dL or GFR ≤30 ml/min) or hepatic dysfunction (evidence of cirrhosis on imaging or AST, ALT or bilirubin ≥3x ULN).
  - Worsening organ dysfunction requiring hospitalization or dose delays occurred in 8 patients (30 %) although in most cases this was thought not-drug related and resolved with supportive care.
  - RR: 15%

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ICB in brain metastases

- Animal models suggest that they may have modest penetrance of BBB
- Ipilimumab (Margolin, Lancet Oncol. 2012;13:459-465)
  - Phase 2 study of (n=72) patients with melanoma and brain metastases
  - No neurological symptoms and not receiving corticosteroids (cohort A)
    - 18% of the patients had disease control at 12 weeks
  - Stable symptoms on corticosteroids
    - 5% disease control at 12 weeks
- Pembrolizumab (Goldberg, Lancet Oncol. 2016;17:976-983)
  - Phase 2 study patients with brain metastases and melanoma and non–small cell lung cancer (PD-L1+)
  - 22% of melanoma patients and 33% of non–small cell lung cancer patients experienced intracranial responses
  - 17% melanoma patients developed grade 3 neurological toxicities

ICB in pregnancy

- PD1/PD-L1 interactions plays a key role in maintaining fetal tolerance;
- Placenta with high PD-L1 expression
- Animal studies: anti-PD1/PD-L1 increased the risks of spontaneous abortions
- Anti-PD1 agents are categorized as pregnancy category D* by the Food and Drug Administration
- Ipilimumab is pregnancy category C*

- * C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- *D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Summary

- Most “special” patient groups can be safely treated with ICB
- Exception: pregnancy (category C or D) and some organ transplants

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