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Immunotherapy in Special Patient Populations

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Topics: Immune Checkpoint Inhibitors in:

- Autoimmune disorders
- Organ transplants
- Chronic viral infections
- Concurrent immunosuppressants
- Organ dysfunction
- Pregnancy
- Brain metastases,
- Pediatric
- Elderly
- COVID-19

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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

Graft Versus Host Disease Associated with ICI: A Pharmacovigilance Study and Systematic Literature Review

- Pharmacovigilance analysis of cases of GVHD associated with ICI in allo-transplant patients
  - 93 cases of GVHD associated with ICI (61.8% men, median age 38y).
  - Cases were mostly associated with nivolumab (53/93, 57.0%), pembrolizumab (23/93, 24.7%) and ipilimumab (12/93, 12.9%) monotherapies.
  - GVHD events occurred after 1 [1; 5.5] injection of ICI, with a time to onset of 35 [IQR = 14; 176] days.
  - Immediate subsequent mortality after GVHD was 24/93, 25.8%.
  - No significant difference in mortality depending on the molecule (p = 0.41) or the combination regimen (combined vs. monotherapy, p = 0.60).
  - Previous h/o GVHD present in 11/18, 61.1% of cases reported in literature.

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Nguyen, Front Pharmacol. 2021 Feb 5;11:619649.

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 steroids 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

- ACCELERATE and European Medicines Agency Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients.
  - High rate of activity of monotherapy checkpoint inhibitors, including complete responses, in Hodgkin lymphoma and hypermutant tumours.
  - Very limited activity of checkpoint inhibitors as single agents in other paediatric tumours (overall response rate–2.8% with Hodgkin's lymphoma excluded).
    - Tumour-associated leucocytes of most paediatric tumours contain few T cells,
    - PD-L1 expression is absent in the majority of tumours (except Hodgkin lymphoma)
    - Contain higher proportions of myeloid cells (macrophages and MDSC)
  - Except for hypermutation, there is no other predictive biomarker.
  - There is no benefit to children to be included in new monotherapy trials of other checkpoint inhibitors with the same mechanism of action unless there is more scientific knowledge.

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Pearson ADJ, Eur J Cancer. 2020 Mar;127:52-66.

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: general statements

- Lung cancer: To date only data provided by non-small-cell lung cancer subtypes are available (low level of evidence). Central response rate on these patients is estimated to be lower than primary site (ORR 17–20%) (low level of evidence).
- Renal cell carcinoma: Only data for clear cell subtypes are available. Responses are achievable only in a very limited number of patients with mono-site small (<1 cm) metastases (very low level of evidence).
- Melanoma: Combination between ICIs seems to be the best treatment strategy in patients with melanoma related brain metastases (BMs) (high level of evidence).
- Other malignancies: Limited data about clinical efficacy on BMs are available. This also includes solid malignancies with high CNS metastases rate (breast cancer and small-cell lung cancer).
- Breast cancer: Breast cancer BM had a lower immune contexture c/w melanoma and NSCLC
- Radiation therapy & ICIs: Recent randomized trials show limited efficacy of the abscopal effect (low level of evidence).
- Combinations between ICIs and stereotactic radiosurgery or WBI are under assessment

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Nunno V, Immunotherapy. 2021 Apr;13(5):419-432.

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.

Immunotherapy in COVID 19 patients

- “Current evidence does not support the notion that ICB therapy worsens complications from COVID-19, and we conclude that it supports the continued use of ICB therapy during the COVID-19 pandemic ” (Garassino and Ribas, Cancer Immunol Res 2021;XX:XX–XX)

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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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