Immune Therapy in Cancer: Checkpoint Inhibition

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Disclosures

- I have received speaking honoraria from Celgene and Amgen.

Overview

- Review how the immune system targets cancer
- Review the mechanisms of action, and efficacy of checkpoint inhibitors: CTLA4 antagonists, PD1/L1 inhibitors.
- Review the pattern of response to checkpoint inhibitors
- Review adverse events and how to manage them.

Immuno-Oncology: Helping your immune system to fight cancer

Surgeon William Coley reported in 1800s that injection of killed bacteria into sites of sarcoma could lead to tumor shrinkage.

Long term survival remain a challenge in many advanced cancers

- Five year survival remains poor for many patients with metastatic solid tumors, Range: 3% to 10% (Seer database).

- There is a need for new treatments and therapeutic modalities for patients with advanced cancers

Evolution of Cancer Therapy

- Surgery
- Radiation (1900)
- Chemotherapy (1940s)
- Immunotherapy (interferons and interleukins) (1990s)
- Targeted therapy (1990s)
- Immune check point inhibitors (2010)

The Arms of Our Immune System

- Innate Immunity: the immediate first line of defense.
- Adaptive immunity: slow to respond, antigen-specific, memory.

Many Types of Immune Therapy in Cancer

- BCG for bladder cancer
- Allogeneic stem cell transplant
- IL-2 (melanoma and renal cell carcinoma): recruit/expand T-cell
- Rituximab (leukemia and lymphoma): recruit macrophages, NK cells, complement.
- Herceptin and Erbitux (monoclonal antibodies): primarily block growth factor signaling to the tumor cells, not immune destruction.
- Ado-trastuzumab emtansine (Breast cancer, Her2+): cytotoxic payload.
- Brentuximab vedotin (Hodgkins, CD30): cytotoxic payload

Activation of T-Cells against Cancer

- Step 1: Antigens are released by tumor cells
- Step 2: Dendritic cells present antigens to T-cells.
- Step 3: T-cell is activated and expanded.
- Step 4: T-cells travel to and infiltrate the tumor microenvironment
- Step 5: T-cells recognize and kill cancer cells
- Step 6: dying cancer cells release more antigens

PD 1/ PD-L1 Inhibition

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CTLA-4 Inhibition

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Check point inhibitors: Key Drugs

- Ipilumumab (Yervoy) (CTLA4): melanoma and renal cell carcinoma
- Nivolumumab (Opdivo) (PD1): many indications
- Pembrolizumab (Keytruda) (PD1): many indications
- Atezolizumab (Tecentriq) (PD-L1): bladder and lung
- Durvalumab (Imfinzi) (PD-L1): Bladder and adjuvant Stage III Lung

Adverse Events: autoimmune: any organ/system

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Adverse Events: autoimmunity

- Within the first few weeks to months of therapy
- Not clear if this correlates to improved tumor activity
- Treatment: stop therapy. High dose steroids with slow taper
- Incidence: 10-25%, serious 1-5%;
- GI: infliximab if steroid-refractory

Personal Experience:

- Coagulopathy: acquired hemophilia A: steroids and Rituxan.
- Hepatitis: treated with steroids.
- Pneumonitis: responded to steroids.
- Pancreatitis
- Myositis

Non small cell lung cancer

- Metastatic disease: Step #1: genomic sequencing, and PD-L1 analysis.
- PD-L1 high (>50% expression): Pembrolizumab alone. Keynote - 024 study. > 300 new diagnosis. 200 mg every 3 weeks vs standard platinum-doublet chemotherapy.
- Progression free survival 10 months vs 6 months. Duration of response 12 months vs 6 months. Overall survival of 30 vs 14 months.
- Adverse events: 27% vs 50%.

Non small cell lung cancer

- Keynote-189 Platin + pemetrexed + pembrolizumab vs chemo alone. All patients, regardless of PD-L1 status.
- 12-month overall survival of 69% vs 49%.
- Improved survival, PFS, and response rate improved regardless of PD-L1 status.
- No trial comparing chemo/pembrolizumab vs pembrolizumab in patients with high PD-L1.
- Consider this triplet in patients with high disease burden requiring quick response.
- Adverse events rate were similar in each arm.

Non small cell lung cancer

- Stage III disease: usually treated with combination of chemotherapy and radiation.
- Five-year survival of 15%
- Durvalumab (Imfinzi); PACIFIC trial NEJM 2017; > 700 patients vs placebo x 1 year.
- Progression free survival of 17 months vs 5.6 months
- 12-month overall survival 83% vs 75%
- May not be beneficial in those with PDL1< 1 %.
- Adverse events (pneumonia) 31% versus 26%.

Small cell lung cancer

- Represents only 15% of all lung cancer.
- Dismal survival rate of only 8-12 months with treatment.
- Highly responsive to doublet chemotherapy but quick time to recurrence.
- Impower133 Study: > 400 patients. NEJM 2018.
- Carboplatin and etoposide and atezolizumab vs chemotherapy alone.
- Median overall survival of 12.3 vs 10.3 months
- Adverse events around 50% in both arms.

Bladder cancer

- Metastatic good performance status: cisplatin-based combination chemotherapy.
- Majority are not candidates for chemotherapy due to advanced age and comorbidities (renal failure, neuropathy, heart failure).
- Pembrolizumab (Keynote-052) > 300 patients. 30% response rate, front line.
- Atezolizumab, Nivolumab, Avelumab, Durvalumab: Phase II studies with a response rate of around 20%, second-line.

Melanoma

- **Metastatic melanoma**; Checkmate 067, > 900 patients
- Nivo + Ipi Q 3 weeks x 4 doses followed by Nivo , versus Ipi x 4.
- Three year progression free survival was 39% vs 10%; overall survival was 58% vs 34%.
- Objective response rate 58% vs 19%.
- Grade 3 and 4 adverse events were 59% vs 28%.
- Pembrolizumab, Keynote-002 Trial. > 500 patients (who had failed Ipi) vs chemotherapy. Response rate of 22% vs 4%.
- Pembrolizumab, Keynote -006 Trial. > 800 patients (new diagnosis) vs Ipi. Overall survival of 42% vs 34%.

Melanoma

- Nivolumab approved by FDA 12/2017 after definitive surgery for **stage III** or IV disease. 480 mg every 4 weeks.
- > 900 patients randomized between Nivo vs Ipi. For 1 year of treatment.
- Relapse free survival at 2 years: 63% vs 50%
- Grade 3 and 4 events, 14% vs 46%
- Ipilimumab vs placebo, EORTC 18071, > 900 patients.
- Relapse free survival at 5 years of 40% versus 30%.
- Overall survival of 65% vs 54% (P = 0.001)
- AEs: Derm, GI, hepatic , 5 treatment related deaths.

Kidney cancer

- Surgical resection can be curative for localized disease, but many recur.
- Small molecule tyrosine kinase inhibitors were and are a major advance in treating metastatic disease.
- Historically only a minority of patients achieved a response to high dose IL-2 or interferon-alfa.
- We risk stratify our patients to help choose therapy.
- Poor performance status, time to diagnosis < 1 year, anemia, high calcium, elevated neutrophil count or platelet count.

Kidney cancer

- Nivolumab vs everolimus who had progressed following prior antiangiogenicc therapy. CheckMate 025. > 800 patients.
- Overall survival 25 vs 19 months. Response rate of 25 vs 5%.
- Nivo (3mg/kg) + Ipi (1mg/kg) q 3 weeks x 4, followed by Nivo vs sunitinib; Checkmate 214 trial.
- Overall survival median not reached versus 32 months.
- Objective response rate 39% versus 32%.
- In the intermediate/poor risk patients OS was significant.
- ***In the favorable-risk patients response rate and PFS was lower***.

Mismatch repair deficient cancer

- Somatic mutations have the potential to encode “non-self immunogenic antigens.
- Tumors with mismatch-repair defects (MMRd) (as in Lynch syndrome) have a large number of somatic mutations.
- Phase 2 study. NEJM 2015. In any patient with MMRd.
- Cohort with colorectal cancer, MMRd, demonstrated improved survival and response rate compared to non-MMRd.
- Objective response rate was seen in > 50% of patients with MMRd across 12 different tumor types. Science. 2017.
- May 2017: FDA approved Keytruda (pembrolizumab) for any adult /pediatric patient with metastatic/unresectable solid tumor with MMRd. – ***a first FDA approval for a tissue agnostic cancer indication***.

Nobel Prize

- Two immunologists, **James Allison** of the United States and **Tasuku Honjo** of Japan, have won the 2018 Nobel Prize in Medicine.
- 1995, Allison was one of two researchers who discovered one of these immune system brakes, called CTLA-4.
- In 1992, Honjo discovered PD-1, another protein on the surface of T cells. In a series of experiments, Honjo showed that PD-1 also works as a T-cell brake.

Hodgkin Lymphoma

- Expression of PDL1 on tumor cells inhibits tumor infiltrating T-cells.
- Amplification of chromosome 9p24 results in overexpression of PDL1 and 2 on the Reed-Sternberg cells.
- Nivolumab (Opdivo), pembrolizumab (Keytruda): relapsed, refractory Hodgkin lymphoma.
- Ansell SM. N Engl J Med 2015; 372: 311-319. 23 patients (s/p ASCT, and BV). RR 20/23 (87%). PFS was 86% at 24 weeks.
- Lesokhin AM. J Clin Oncol 34:2698-2704. 2016. Phase Ib in relapsed / refractory hematologic malignancies. 81 patients: FL (40%), DLBCL (36%).

Checkpoint Therapy and Response Evaluation

- Treatment beyond progression. Estimated that around 10% may respond despite progression on scans.
- Don’t scan too early, if you do, consider continuing therapy and rescanning.

Immunotherapy clinical trials (at University Hospitals)

- Metastatic and Adjuvant therapy in esophageal cancer
- Adjuvant therapy in breast cancer (triple negative) after neoadjuvant therapy.
- Bladder cancer: neoadjuvant with chemotherapy
- Small cell lung cancer (extensive stage disease)
- Non small cell lung cancer (with targeted agent)

Science Fiction?: CAR- T cells

- Chimeric antigen receptor
- FDA approved in relapsed ALL (CD19) August 2017.
- Limited number of centers
- $500 K / procedure
- Cytokine release syndrome.

Tisagenlecleucel in Adult Relapsed/ Refractory DLBCL NEJM 1/3/2019

- Phase II study with at least 2 prior therapies
- Ineligible or disease progression after Auto Stem Cell Transplant
- No prior allogenic transplant
- Primary end-point: overall response.
- 93 patients infused. 14 month follow up.
- 40% complete response rate, 12 % partial response rate
- At 12 months follow up, 65% relapse-free.
- Cytokine release syndrome: 22%

- Thank you, and enjoy the Snow!