Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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Disclosures

- Consultant for Reata Pharmaceuticals
- I will not be discussing non-FDA approved indications during my presentation.

Immunotherapy and Cancer: Critical Questions

IMPORTANT CAVEAT: Not all immunotherapies are the same!! Some therapies such as Checkpoint Blockade (ie targeting PD1/PDL1 or CTLA4) require an active immune system to mediate effects. Others such as CAR T cells are passive and the engineered cells do all of the anti-tumor effects and may require immune suppression of the patient. As immunotherapy is being more and more used it is critical not to lump as all one therapy. Also- we still do not know what the mechanisms underlying these effects are.

Question: When and how to use immunotherapy in cancer depends on the cancer, the patient and the type of therapy. How to decide what to use, when to use it and on what patients are key questions.

Immunotherapy and Cancer: Critical Questions

- HOW DO WE BETTER SELECT PATIENTS FOR RECEIVING IMMUNOTHERAPY AND WHAT TYPE? What type of cancers should be targeted?
- Status of the tumor: high mutation load, presence of immune infiltration (ie “hot”), presence of particular markers (ie PD1/PDL1 for checkpoint block). Extent of the tumor spread or tumor burden. Presence or absence of tumor-specific targets (which can play a role in off-target or toxic effects).
- Immune status of the patient as active immunotherapy (ie checkpoint blockade, vaccines, oncolytic virus therapies) need a robust immune response for significant and (importantly) sustained effects.
- Other patient parameters such as body mass index (BMI), age, gender, presence of co-morbidities all have been shown to impact immunotherapy outcome, both positive and negative.

Immunotherapy and Cancer: Critical Questions

- Given that immune therapies involve immune activation and tissue attack, potentially to distal sites (where metastasis exists): How can one minimize the toxicities and off-target effects associated with immunotherapy?
- Not all immunotherapies have the same toxicities and it is unclear as to why some patients present with some toxicities although likely factors such as: genetics, age, immune system status, tumor burden, con-current or previous treatments and co-morbidities all contribute.
- There is a need to understand both short and long-term effects of cancer immunotherapy, both positive (against the tumor and possibly to other pathogens) and negative (later induction of immune deficiency or auto-immune attack).

Immunotherapy and Cancer: Critical Questions

- How do we determine WHEN to give immunotherapy? Early? Late? At what stage? When to give other treatments (ie radiation, surgery, chemotherapy) as may interfere with immune outcome?
- How long to give immunotherapy?? When does one stop given that cancer can become dormant? Does the immunotherapy need to be continuously given once the “brakes” are off?
- What is the goal of immunotherapy: eradication or control? How can we circumvent cancer immune evasion?
- How done one determine cost-benefit ratio of each type of immunotherapy to the patient?

Issues in Immunotherapy

- Cost- with some immunotherapies costing over $500,00 for treatment, how can fiscal toxicity be managed and accessibility still occur given that immune therapies can be costly to both generate (ie CAR T cells) and manage toxicities (cytokine storm, auto-immune attack etc).
- Multiple drugs/reagents are developed that can target the same pathway. How does one decide which to pursue or trial to participate in?
- Application length is usually determined by toxicities. If lesser toxicities result, what is considered appropriate end-point (ie compared to hormonal therapies)? How should patients be monitored for immune effects outside of the cancer?

Issues in Immunotherapy

- There is a tremendous need for antigen-specific therapies for common solid tumors (ie breast cancer, colon cancer, prostate cancer, pancreatic cancer) without overwhelming toxicities do to normal tissue attack. This may dictate types of immunotherapies that can be applied as the nature of tumor antigens targeted in checkpoint blockade is not known.
- The mechanism by which checkpoint blockade works in some patients is not clear but sustained responses indicate that continuous immune activation, adaptation and attack may occur.

Future Directions for Immunotherapy

THE KEY WILL BE TO BETTER UNDERSTAND THE IMMUNE SYSTEM IN GENERAL IN ORDER TO DETERMINE HOW BEST TO MANIPULATE IN CANCER

- Optimization of cell engineering resulting in greater effects
- “Off-the-Shelf” cell therapies being developed
- Combination approaches with other immunotherapies being applied
- Determination of what cancers and cancer sub-types respond as well as tailoring to individual immune status
- Targeting cancer stem cells and dormant cancer cells
- Development of cancer vaccines (with possible application with modulating agents)

Future Directions for Immunotherapy

- How can we better arm and maintain our immune system so as to allow for sustained immune responses to occur in cancer?
- Development of means to determine immune status of a patient (which is constantly changing even with simple aging).
- Determining means to develop optimal immune “health” (ie diet, life-style etc) and understanding how aging affect these parameters are critical to apply immune therapies.