The earliest reports of harnessing the body’s immune system to fight tumors involved injection of bacterial products (Cooley’s toxin) into patients which triggered the release of cytokines against endotoxins and, subsequently, resulted in shrinkage of tumors. These concepts were refined in the last 1970s and 1980s with the introduction of recombinant IL-2 into clinical practice for the treatment of renal cell carcinoma and melanoma. Treatment with IL-2 was associated with objective response rates of 20% and durable responses in 5-10% of patients with melanoma. The success with IL-2 was a proof principle and generated much excitement. As IL-2 elicits tumor response and T-cell activation in an overall non-specific way, the heterogeneity of response was puzzling. Moreover, treatment with IL-2 was associated with significant toxicity. As such, efforts were made to improve patient selection to minimize unnecessary exposure to toxicity in patients unlikely to respond. Through these efforts, PD-L1 expression (or an immune rich environment, high serum VEGF and fibronectin, and MAPK pathway mutations emerged as predictive biomarkers. Specifically, PD-L1 expression was associated with benefit and response rates with NRAS and BRAF mutations were 40% and 23% compared with 18% in those wild type for these mutations.

More recently, efforts have been made to enhance specificity of immune activation. Adoptive cell therapy refers to the isolation of tumor infiltrating lymphocytes from tumors, expansion of these T-cells with exposure to IL-2, and re-infusion of the tumor infiltrating lymphocytes in patients after lymphodepletion. Lymphodepletion usually uses myeloablative chemotherapy (Cytoxan and fludarabine) and works in part to deplete Tregs which might counteract the T-cell transfer as they too are stimulated by IL-2. Initial reports of adoptive cell transfer reported response rates of 40-60% but this is likely reflective of a selection bias for subjects able to travel to the NCI with tumors that were able to grow TILs. The intention to treat response rate is likely closer to 29%. T-cell engineering has also been employed to enhance tumor recognition. Methods used include tumor analysis/computational analysis to select TILs, engineer more specific T-cell receptors, and chimeric antigen T-cell receptors (CAR-Ts). Objective response rate to CAR-Ts in melanoma ranged from 19-30%. Finally, early efforts to enhance tumor recognition with vaccines were unable to trigger an adequate inflammatory response. More successes, however, are expected with newer engineered vaccines. For example, there have been promising results with the recently approved T-VEC, a vaccine which is coupled with GM-CSF facilitating recruitment of dendritic cells. This vaccine was associated with an objective response rate of 50% and is most likely to be most useful for treatment of locally advanced, inoperable melanomas. Combination of TVEC and other vaccines with checkpoint inhibitors is also a promising strategy that should be explored.
Current iterations of ACT are focused on improving response rate beyond that achieved with traditional TIL therapy alone. Multiple strategies have been developed including the addition of immune checkpoint modulators or passive immunization. Clinical trials based on these concepts are currently testing TIL combinations with PD-1 (TIL/MK-3475), CTLA-4 (TIL/pilimumab), DC vaccines (NCT00338377) or allogenic cell-based tumor antigen expressing vaccine (Viagenpumatucel-l/HS-110). Ultimately, these strategies are still dependent on the ability to generate (and expand ex vivo) an autologous T-cell population and on the ability of the transferred T-cell to recognize tumor associated antigens and mount an effective T-cell immune response unfettered by the tumor microenvironment.

T-cell engineering has permitted the generation of chimeric T-cells that consist of an ectodomain (containing signal peptides and antigen recognition regions separated by a spacer), transmembrane domain and an endodomain - latter two are typically CD3-zeta transmembrane and endodomains. Utilizing specific chimeric immunoreceptors (CAR) (CD19/CD20 - B-cells), engineered T-cells are able to selectively home in and permit T-cell mediated cytotoxicity. The promise of this approach was illustrated by several clinical trials that demonstrated efficacy of CD19-targeted CAR in patients with relapsed/refractory acute lymphoblastic leukemia (ALL) and myeloma2-3. This strategy has been extended further with the elaboration of 2nd and 3rd generation CAR T-cells that possess one or more intracellular signaling domains (CD28, 4-1BB, OX40) to augment anti-tumor effect.

Given the well-established role of the tumor microenvironment in mediating primary and acquired resistance to T-cell immunotherapy, investigators studying both checkpoint inhibition and ACT have sought to improve upon results by targeting various elements of the tumor microenvironment. One component that has been the subject of intense interest is transforming growth factor beta (TGFβ) - a T-cell cytokine heavily implicated in inhibiting T-cell activation, proliferation and cytotoxicity. In murine models, T-cells rendered insensitive to TGFβ by transduction with TGFβ dominant negative receptor II, were highly effective in eliminating established melanomas4. Efforts at targeting TGFβ to augment TIL efficacy have focused on re-engineering T-cells to express TGF-β1-dominant negative transgene (NCT01955460) rather than utilizing monoclonal antibodies (fresolimumab/GC1008) to target TGF-β.

Extending the scope of TIL beyond select melanoma, ALL and myeloma patients requires concurrent advances in two areas. Although promising, ACT is associated with exorbitant costs and tremendous laboratory expertise – which precludes widespread commercialization (and uptake) in the current reimbursement model. Identifying and implementing process automation may serve to improve scalability and cost – an approach which is actively being evaluated by several investigators5. Secondly, alternative targets (such as Her-2/neu) have to be identified and validated to permit the extension of this approach to tumor systems beyond melanoma and the hematological malignancies. However, target identification and validation has to proceed concurrently with evaluation of target expression in non-tumor tissue to mitigate ACT adverse effect profile such as previously seen with use of T-cells targeting ERBB2/Her-2/neu in a patient with advanced breast cancer6.

Bibliography

Cancer immunotherapy has been gaining recognition as key cancer therapeutics in the past two decades and it was initially pioneered by Dr. Steven A. Rosenberg at the National Cancer Institute. Cancer immunotherapy is a therapeutic modality that utilizes and manipulates one’s own immune system to eradicate cancer. The first immunotherapy, a recombinant Interleukin-2, was approved by the FDA in 1970’s. Since then, particularly in the last 5 years, there have been various immunotherapeutic agents that have been approved by the FDA.

Interleukin-2 stimulates the immune system in a non-specific manner. It activates the immune system, increases lymphocyte count, and enhances humoral and cellular immunity. It has been described as “pouring gasoline on a match” and it intensifies immune reaction in such a dramatic way that it can be accompanied by several toxicities. One of the most notable toxicity is capillary leak syndrome, where patients can develop anasarca and pulmonary edema. It essentially causes a massive inflammatory reaction similar to a patient in septic shock and the patient can have end organ damage, although all these effects are dose dependent and completely reversible. Interleukin-2 is approved for treatment of malignant melanoma and renal cell cancer.

There are other agents that are more specific in terms of their mechanism of action. Ipilimumab, for instance, is a monoclonal antibody targeting anti-CTLA 4, an immune inhibitory receptor. It works by inhibiting the “breaks” on the immune system. It was approved by the FDA in 2011 for the treatment of malignant melanoma. Some of its side effects are autoimmune conditions, such as colitis or hypophysitis.

Another immunotherapeutic agent currently in the market is anti-PD-1 monoclonal antibody for the treatment of malignant melanoma and non-small cell squamous cell lung cancer, approved in 2014 and 2015, respectively. It works by blocking a negative regulator on T-cells thus allowing the immune system to attack cancer. In other words, it blocks PD-L1, T-cell negative regulator, from binding to PD-1, allowing T-cells to recognize and attack the tumor.

Adoptive cell therapy involves transfer of autologous cells with cancer fighting property into the patient. The cells being transferred can either be autologous tumor infiltrating lymphocytes selected and expanded ex-vivo or autologous lymphocytes engineered with TCR or CAR targeting a particular tumor specific antigen. Other examples of immunotherapy are cancer vaccine and intra-tumoral injection of talimogene laherparepvec (T-VEC), both of which have shown some promising results.

Immunotherapy is an area of cancer therapeutics that is rapidly evolving and there are many ongoing clinical trials. It has become an important armamentarium in the treatment of cancer along with receptor-associated kinase inhibitors.

There is a history of immunotherapy, starting with the use of erysipelas inoculation as a “cure” for cancer back in the early 1900s by Dr. Coley, which may have worked in some cases due to the release of cytokines from the inoculation. Of course, this also led to infection and death, but was likely the first proof of principle. A more recent proof of principle is IL-2 for metastatic melanoma, for which in a subset of patients this results in at least a prolonged remission and likely cure. A third example is the more recent use of PD-1 and PD-L1 inhibitors in a range of cancers which results in prolonged responses in a subset of patients.

The mechanisms underlying the immune response to malignancies are likely mostly due to T-cell activation and activity. Th1 cells (stimulated by IL-12 and IFN-gamma) are thought to be the predominant cell involved in anti-tumor activity, with T cell receptors that bind tumor specific antigens. On the other hand, Th2 and Tregs are associated with increased tolerance lack of anti-tumor activity. IL-2 is FDA approved as treatment in RCC and melanoma, with demonstrated long-term survival (and complete responses) in a small subset of cases, a short defined treatment course, and limited long-term adverse effects. The major issues with treatment are 1) toxicity (e.g. administration requiring inpatient MICU level support) and 2) the relatively small number of patients who have durable benefit. Attempts to address this issue have included attempts to find biomarkers which enrich for responders (e.g. different gene expression signatures, markers of immune infiltration, NRAS mutation).
A second approach is adoptive T cell therapy, where tumor along with associated immune infiltrate is harvested, co-cultured with IL-2 (to stimulate Th1 growth), then populations assayed for specific tumor recognition. These are then selected and expanded, then transfused back into the patient following a lymphodepletion/preconditioning regimen, with a significant response rate (30-50% in melanoma and cervical cancers), but without sustained response. Current efforts to improve on this approach include engineered T-cell receptors for increased specificity to tumor neoantigens, and chimeric antigen receptor (CAR) T cell receptors for specificity to tumor cell antigens (may not be neoantigens). This has been quite successful in a number of hematologic malignancies, but results have not yet demonstrated in solid malignancy, and also have been associated with significant toxicity due to attack on normal cells expressing similar antigens.

A third cellular approach is to enhance tumor recognition via vaccines – two approaches being a local approach (e.g. introducing an engineered herpes virus locally that enters tumor cells preferentially and co-express GM-CSF) which has a local effect, or inducing a systemic effect. “Radiation as vaccine” is the concept of cancer cell death from radiation leading to immune activation with increased exposure to neoantigens, also known as the “abscopal effect” (i.e. tumor response in areas separate from where radiation is directed).

In sum, immunotherapy has a long history of dramatic impact in limited subsets of patients with cancer, but great strides are being made in further developing this technology to help a greater number of patients as well as reduction in toxicity. The story is still developing!

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In Dr. Ryan Sullivan’s talk on cellular therapy and cancer related vaccines we reviewed the history of immunotherapy going back to the role of Dr. Coley’s toxin (Erysipelas) as a means of facilitating tumor response. The more recent examples include other immune adjuvants like IL-1 and GM-CSF. Other cytokines like IL-12, IFN-gamma and IL-2 may be of potential use but their utility is still poorly characterized. Concerning features of cytokine therapy include the extensive list of toxicities that require MICU level support to engender treatment response. Durable responses in patients with melanoma and RCC can occur in as much as 5-10% of patients. Treatment selection for cytokine therapy seems to mirror that of checkpoint blockade approaches with PD-L1 and B7-H3 positive tumors exhibiting the highest response rate.

Adoptive Cell Therapy (ACT) has shown great potential but is technically challenging and has largely moved to 2nd and third line in the triaging of immunotherapy regimens given these issues. Some of the technical issues really pertain to the fundamental problem of defining which tumor antigens seem to result in tumor cell kill. Additionally, vascular access seems to be an issue in some contexts and can limit the accessibility of therapeutics and infiltrating cells to sites of disease.

An additional area of interest is the use of hypofractionated radiotherapy to generate antigen release and an immune response. This has some promise with metastatic melanoma and a recently published study in Lancet Oncology using a Simon’s Two Stage design. This approach seems to benefit from the addition of either a checkpoint blockade strategy or the use of an additional immune adjuvant such as GM-CSF.

In summary tumor immunotherapy seems to have a promising future in select populations thus adding an additional weapon to the war chest of oncologists.

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In his address to the STOFF participants, Dr. Ryan Sullivan presented a thoughtful overview of historic, recent, and emerging technologies in immunotherapy. Topics discussed included the interaction of proteomic and pharmacogenomic biomarkers and response to high dose interleukin-2. Among more recent developments, techniques and evidence for adoptive T cell transfer and chimeric antigen receptor (CAR) T cell therapy were presented. A very interesting and timely point was the discussion of immunotherapy for melanoma using oncolytic HSV with an embedded GMCSF encoding construct (talimogene laherparepvec, or T-VEC). Based largely on clinical evidence that Dr. Sullivan also featured in his talk, the FDA approved T-VEC only days after the conclusion of the 2015 STO fellows’ forum.

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