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If tumor changes the tune, we change the music

In 1985, after operating on President Ronald Regan for Colon Cancer, Steven Rosenberg went home and saw "Silverado." Cool under the spotlight for operating on his VVIP patient, he was to remain in spotlight for next 30 years for his work and his team for bringing adaptive cell therapy (ACT) to the lofty goal of eradicating difficult to treat cancers.

Recently, in a new clinical trial by Zakaris *et al*. (including Steven Rosenberg), a 49-year-old patient with ER-positive (ER+) and ERBB2 tyrosine kinase 2 negative (HER2-) metastatic breast cancer that was no longer responsive to other treatments was reported to show complete regression of the cancer. She was part of a clinical trial that was designed to determine if autologous tumor infiltrating lymphocytes (TIL) could have an effect on epithelial tumors that have undergone metastasis. The trial involved a modified ACT approach wherein the researchers sequenced DNA (whole exome sequencing) and RNA from one of her tumors, as well as normal tissue to derive the tumor mutational burden (TMB). On comparing the sequences in the tumor and normal tissues, they identified in the tumor cells 62 mutations that were acquired and non-synonymous (mutations that altered the amino acid sequence of the protein). Tumors with a higher TMB (hers was higher than the average for similar ER+HER- breast cancers) are more likely to respond to TIL therapy. Of the 62 mutations (neo-antigens), the patient's TILs recognized four of the mutant proteins. These specific autologous TILs were selected, enriched, and expanded and were infused back into the patient. To prevent any possibility of activation of the infused T cells on entering the tumor, she was given the checkpoint inhibitor pembrolizumab as well. Cancer completely regressed, and she remained tumor-free even 22 months later.[1]

Metastatic breast cancer that has evolved multiple mutations no longer remains treatable by chemotherapy or monoclonal antibodies and a personalized TIL Cocktail created to specifically target that patient's mutations is a crucial new paradigm in the difficult journey of this otherwise incurable stage.

Inter- and intra-tumoral heterogeneity has been a hurdle to overcome in performing reductionist cancer therapies. The molecular make-up of different tumors is different, and even within the tumor, there are a variety cancer cells that differ from each other molecularly. Hence, by targeting individual cells, we cannot conquer every tumor cell. In personalized cancer medicine, homing in on individual mutations would be overwhelming with the broad range of mutations between and within individuals.

Immunotherapy, on the other hand, is a step back from the ultra-molecular level approach. It allows one to overcome the issue of tissue heterogeneity (tumor "mutanome"/neo-epitopes). ACT involves TILs extracted from a patient's own tune [schematic shown in Figure 1]. These autologous cells are already capable of recognizing the patient's repertoire of epitopes, so they are a highly personalized form of therapy. The extracted TILs are cultured, selected (for tumor specificity) and expanded before re-infusing into the patient who has in the meantime undergone lymphodepletion.

Initially, cleared for use in metastatic melanoma, TIL therapy is undergoing clinical trials in various other tumors. Unlike chimeric antigen receptor (CAR)-T cells, which can only recognize extracellular antigens, TILs can recognize extracellular and intracellular antigens and have a higher objective response rate (around 50%) in clinical trials thus far. However, unlike the response seen in melanoma, thus far, epithelial cancers such as breast cancer did not respond as well to this therapy.

Cancer therapy has progressed in painful increments. It began with cytotoxic chemotherapy non-specific to tumor molecular biology but having the capacity to reduce dividing cells. Next came the era of monoclonal antibodies (Herceptin and rituximab) which worked wonders but were incapable of predicting and treating developing new mutations in patients who failed to respond or recurred. Furthermore, there were targeted therapies such as tamoxifen in late 80 s and imatinib in early 2000 which promised on targeting biochemical process steps inherent to cancers. Again they were helpless in predicting what new obstacles may be put up by an evolving mutating tumor. Last decade saw the arrival of immunotherapies and dramatic advances with PD inhibitor and CLTA4 manipulators. In the same arena now comes this dramatic report of the ACT.

ACT is a treatment using patients own lymphocytes with anti-tumor activity, expanded *in vitro* and reinfused. Lymphodepletion before ACT is crucial as it eliminates Tregs and other lymph which compete for cytokines (interleukin [IL]-7 and IL-15). Lymphodepletion makes sure ACT is long term.[2] Tantalizing possibility that lymphodepletion opens mucosal surfaces to commensal microorganisms that activate Toll-like receptors to "turn on" APCs to provide backlash anticancer recognition and destruction! Takes us back to "Coley's Toxins" which were postulated to cure cancers over a century ago.[3]

In breast cancer, worse the tumor type (HER2 and TNBC) more the correlation of higher TILs with higher pCR. This may indeed become a surrogate for Early HER 2 +(<1 cm) breast cancers for the decision to use Herceptin. TIL in residual

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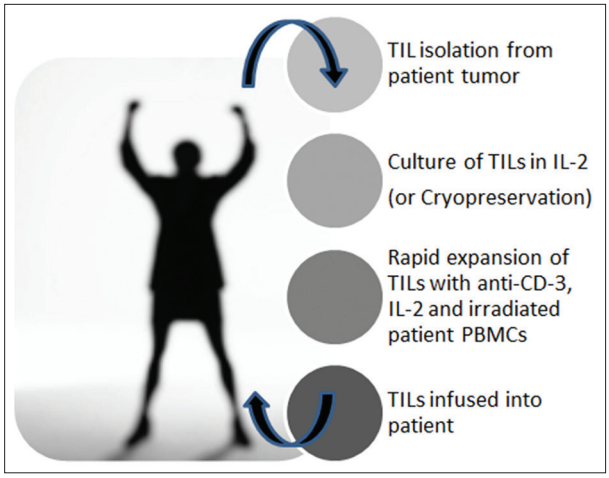

Figure 1: A schematic of the immunotherapy described

disease may aid in the selection of adding immunotherapy in patients not achieving PCR.[4,5]

For breast cancer, this is very welcome news. TILs have so far not been an easy target to work within breast cancer. The CAR-T, a therapy already approved for acute lymphocytic leukemia and certain lymphomas, is an example of the ACT whereby a gene for CAR is inserted in pheresed T cells and thus empowered, reinfused into a patient for eradicating cancer.

How one provides individualized ACT to patients, who pays for it, the role of Governments and Institutions like NCI in making this available are going to be the next challenges. Certainly recent pricing of CART Rx by Pharma to nearly half million dollars suggests this is not the path to future as it will be unsustainable.

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