IN THE SPOTLIGHT

Making the Most of Cancer Surgery with Neoadjuvant Immunotherapy

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Summary: Surgery remains our strongest treatment pillar against early stages of cancer. In a number of instances, the curative potential of surgery can be enhanced by treatments given before (neoadjuvant) or after (adjuvant) surgical procedures. Immunomodulation has emerged as a powerful tool to fight metastatic disease across cancer histologies and goes now to be tested at earlier surgically amenable stages. The work by Liu and colleagues in this issue provides solid preclinical evidence in support of neoadjuvant immunotherapy over adjuvant approaches. *Cancer Discov; 6(12); 1312–4. ©2016 AACR.*

See related article by Liu and colleagues, p. 1382 (7).

Cancer surgery is the treatment of choice for localized disease with the objective of achieving a surgical margin-free complete resection of the tumors. Procedures also usually involve lymphadenectomy seeking to remove metastatic and micrometastatic lymph nodes in the areas draining tumor tissue. Patients are frequently declared to have no evidence of disease based on postsurgical imaging techniques and pathology examination of the excised specimens, but a significant number of cases relapse at different intervals either locally or distantly with regard to the removed primary malignant lesion.

Starting with breast cancer (1) and followed by other diseases, evidence has been found that the adjuvant instigation of oncology anticancer therapies such as chemotherapy, radiotherapy, or targeted therapies following surgical healing statistically decreases and delays relapses, presumably dealing with minimal residual disease. In other studies, pharmacologic and radiotherapeutic treatments are delivered before the surgical procedure with the aim of cytoreduction, with a number of instances in which there is obvious long-term survival benefit that has turned neoadjuvant courses of treatment state-of-the-art.

In recent years, immunotherapy has been witnessing rapid progress that has resulted in more than nine FDA and European Medicines Agency approvals for immunotherapy agents targeting the PD-1/PD-L1 and CTLA-4 axes with immunomodulatory antibodies also known as checkpoint inhibitors (2). Success over standard of care as a second line of treatment against metastatic disease has resulted in trials testing the efficacy to prevent or delay relapse following surgery in cases with high probability of relapse in melanoma (3), non–small cell lung cancer (NSCLC; for instance, NCT02595944 and NCT02504372), and other indications. These studies will tell in time if adjuvant immunotherapy with these agents is worthy of changing medical practice.

Neoadjuvant schemes are also under scrutiny in relatively small series of patients. These studies offer the possibility to make observations on the excised tissue to draw important mechanistic conclusions for the development of these extraordinary novel agents. Over 60 studies exploring checkpoint inhibitors (anti–PD-1/PD-L1 and anti–CTLA-4) as neoadjuvant strategies are now ongoing in several tumor types, including melanoma, NSCLC, bladder cancer, renal cell carcinoma, ovarian cancer, prostate cancer, gastroesophageal cancer, colorectal cancer, mesothelioma, pancreatic cancer, triple-negative breast cancer, and glioblastoma (Clinicaltrials.gov). Some of the main objectives of many of these studies are response rate and pathologic response rate following neoadjuvant therapy. Pathologic response rate is considered a major endpoint to estimate treatment efficacy in chemotherapy neoadjuvant studies in many tumor types. Yet, it remains to be seen whether response rate will truly capture the potential benefit on long-term survival of immune-checkpoint inhibitors administered preoperatively.

The field of immunostimulatory mAbs is not restricted to those tampering with inhibitory receptors (checkpoint inhibitors) such as CTLA-4, PD-1/PD-L1, LAG3, TIM3, TIGIT, and others. There is also a family of mAbs that agonistically act on TNFR family members that costimulate T and natural killer cells (4). These include antibodies against 41BB (CD137), OX40 (CD134), and anti-GITR (CD357) that are undergoing clinical trials (4). It is actually remarkable that immunostimulatory mAbs are often highly synergistic when used in combinations that are under clinical scrutiny and have resulted in the approval of a nivolumab plus ipilimumab regimen for the treatment of metastatic melanoma (5). In this regard, combinations of PD-1 blockade with agonist anti-CD137 mAbs offer outstanding efficacy in preclinical models, either transplantable or spontaneous (6).

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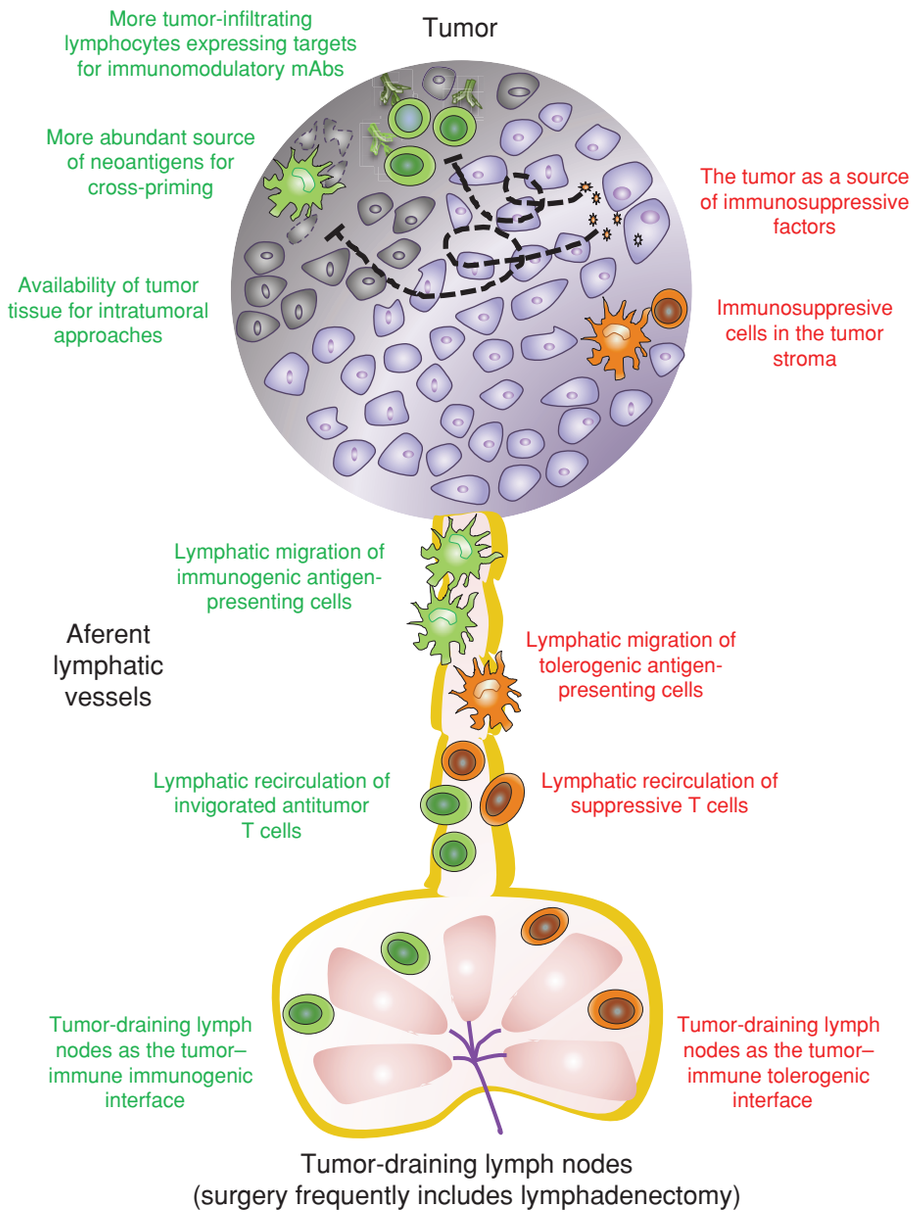

Figure 1. Pros and cons for neoadjuvant immunotherapy. Schematic representation of factors in favor (green) and against (red) the efficacy of neoadjuvant immunotherapy from a mechanistic point of view. In order to make the most of surgery plus immunotherapy strategies, all of these factors are to be taken into account, and we postulate that regimens encompassing both neoadjuvant and adjuvant dosing will be the most efficacious.

The study from Liu and colleagues (7) asks a most relevant question in regard to combining radical surgery and immunotherapy in cancer preclinical models: Should we instigate immunotherapy before or after surgery?

To answer the question, they use two transplantable models of breast cancer that are spontaneously metastatic to the lungs. In these settings, three immunomodulatory mAbs are tested: anti-CD25 mAbs or other experimental strategies to remove regulatory T cells, anti–PD-1 mAbs to block its checkpoint activity (3), and anti-CD137 to costimulate T cells (4). Of these treatments, the authors pick the anti–PD-1 plus anti-CD137 mAbs combination as the most effective treatment, but with all of them, a better survival beneficial effect is seen when treatment is given before surgery. Very elegant experiments rule out that this was due to reduced tumor burden, because delay of surgery in the presence of neoadjuvant immunotherapy treatments still improves survival and reduces metastatic tumor burden in the lungs. Accurate measurements of the $CD8^+$-mediated antitumor immune responses go on to confirm that more robust antitumor $CD8^+$ T-cell responses are observed with neoadjuvant regimens, as compared with adjuvant applications. This is in keeping with the absolute requirement of $CD8^+$ T cells and IFNγ for the therapeutic efficacy of neoadjuvant treatments in these models.

In mice, transplantable tumors progress at a rate that limits time-to-observation periods, but it is of note that an interval of only 2 days before surgery confers the neoadjuvant effect in these preclinical models. Such short time frames suggest excellent translational development potential in humans, with minimal actual delay of surgical operations (if any).

From an immune mechanistic point of view, several features are clearly in favor of neoadjuvant application (Fig. 1):

- Tumor-infiltrating lymphocytes are present that are often the majority of cells expressing the targets for the immunomodulatory mAbs in the organism (8).
- There is abundance of tumor antigens available for cross-priming (9) at the time of immunotherapy.
- There could be recirculation of reinvigorated T lymphocytes out of the primary tumor infiltrate to tackle metastatic disease.

On the other hand, the tumor microenvironment is thought to be teeming with cellular and molecular immunosuppressive elements that could hamper immunity, and therefore surgical debulking would lessen such undesired mechanisms.

An important issue to be considered is how to deal with lymphadenectomy, as draining lymph nodes are critical sites for T-cell priming and antigen presentation. It is conceivable that if sufficient time is given between neoadjuvant immunotherapy and surgery, the function of draining lymph nodes would have been already accomplished, at least to some extent, by the time of lymphadenectomy.

It would also be of great interest if the neoadjuvant advantage is also to be seen with ablative radiotherapy, altering the so-called abscopal effects against micrometastatic disease. However, in the case of radiotherapy, other considerations must be kept in mind, such as immunogenic tumor cell death leading to the generation of an *in situ* vaccine to be potentiated by adjuvant or at least concomitant immunotherapy (10).

A question that remains is whether we have to actually choose between neoadjuvant or adjuvant immunotherapy. It is likely that the best approach would be to instigate combined immunotherapies encompassing both neoadjuvant and adjuvant treatments. For instance, we are conducting a clinical study in surgical cases of patients with glioblastoma multiforme to whom nivolumab is given both before and after neurosurgery (NCT02550249).

Following the provocative mouse studies in this issue (7), clinical trials are warranted that should compare adjuvant, neoadjuvant, and combined neoadjuvant plus adjuvant regimens. Neoadjuvant immunotherapy makes much sense and now has very strong comparative preclinical evidence to back it.

Disclosure of Potential Conflicts of Interest

I. Melero is a consultant/advisory board member for Alligator, Bristol-Myers Squibb, Lilly, Merck Serono, Novartis, and Roche. No potential conflicts of interest were disclosed by the other authors.

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CANCER DISCOVERY

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