The Potential of Neoadjuvant Therapy in the Treatment of Solid Tumors

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As the science of treating cancer in its many forms continues to advance and evolve, neoadjuvant therapy has gradually become viable in some settings. Today, this approach is well-established in treating breast and colorectal cancer, just as two examples, with patients being treated with various agents before surgery. We are now exploring the onset of neoadjuvant therapy and its potential for treating other cancers, including non-small cell lung cancer (NSCLC), head and neck, and gastrointestinal tumors.

For NSCLC patients, 60-70% are diagnosed with late-stage disease, where curative treatment is not yet available. Unfortunately, even the resectable patients have a high risk of relapse and a shorter overall survival compared to other solid tumors.[1] Historically, neoadjuvant chemotherapy has very limited benefit in resectable NSCLC, although adjuvant platinum-based chemotherapy after complete resection added modest (5%) improvement in overall survival for patients.[2] Recently, chemotherapy combined with immune therapy is under investigation in perioperative care of resectable NSCLC.

An important trend

This is possible largely because of the advent of new classes of agents, including targeted therapies and immunotherapies such as drug conjugates, monoclonal antibodies, and checkpoint inhibitors, in addition to chemotherapy. Until now, it has not been clear whether relevant toxicity would result from immunotherapy combined with chemotherapy. Further, the neoadjuvant approach has been disappointing with chemotherapy treatment only.

1 Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 71:209-249, 2021.
2 David O'Reilly, et.al., Treatment Decisions for Resectable Non–Small-Cell Lung Cancer: Balancing Less With More?, ASCO Educational Book, 2023.

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Recent trials confirmed significant benefits with increased disease-free survival data with adjuvant and neoadjuvant immune-chemotherapy and showed greater pathologic complete response in resected NSCLC tumors.[3] It is important to note that there was no significant delay of surgery due to the neoadjuvant therapies, and the treatment-related toxicities were manageable. Adjuvant immune therapy and neoadjuvant immune chemotherapy are now approved therapy options for patients with resectable NSCLC without driver mutations.

This is an important trend for many reasons, not least because of the potential for researchers to examine tissues before and after treatment without subjecting the patient to multiple biopsies. The initial diagnosis is based on a single diagnostic biopsy: a pretreatment tumor sample. Researchers can interrogate the tissue after it has been exposed to these treatments after the surgery. This provides opportunities for molecular exploration of a sample to determine the effect of the treatment on the body after surgery, potentially revealing mechanisms of resistance and reasons for the response. Further, these developments have positively impacted our diagnostic paradigm.

In the clinical trial, we can establish when the therapy will positively affect the outcome and how we should subsequently use it in the neoadjuvant setting. That is one critical role of clinical trials: to provide proof of improved outcomes for the patient to make this approach the standard of care.

Further, new imaging techniques enable early screening of patients who might qualify for neoadjuvant therapy. We are now more likely to be able to diagnose and treat patients in the resectable stages before the disease has advanced. This is especially important in NSCLC because early screening has not been an available option in the past.

In July 2021, pembrolizumab (Keytruda) received FDA approval for the treatment of high-risk, early-stage triple-negative breast cancer (TNBC).[4] This approval was based on data from the phase 3 trial, KEYNOTE-522, which included 1,174 patients with varying tumor stages and nodal status. The trial demonstrated that adding pembrolizumab to neoadjuvant chemotherapy, followed by adjuvant pembrolizumab monotherapy, significantly improved outcomes for patients with high-risk TNBC. This treatment approach is now considered one of the standard options for patients with TNBC, particularly those presenting with T2 tumors or N1-positive breast cancer, which are associated with a greater risk of recurrence compared to other histologies.

Although the KEYNOTE-522 trial demonstrated improved outcomes with the addition of pembrolizumab to aggressive chemotherapy, not all patients may require such intense therapy. Biomarkers that can predict response to treatment are still under investigation and require further research. Currently, response assessment in the neoadjuvant setting, including MRI evaluation or evaluation of residual tumor in the surgical specimen, can provide important

3 Ibid.
4 FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer | FDA

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predictive information for patient survival in TNBC. These simple clinical evaluations may serve as practical tools to spare patients from side effects and financial burden until more precise biomarkers are identified.

Considerations for trial design

With neoadjuvant therapy, the aim is always to get better control over the tumor and reduce the risk of early relapse after complete resection, perhaps achieving some shrinkage before surgery. Yet, by the same token, the effects of the treatment on the tumor and vascular supply to the tumor can cause challenges for surgeons. We must consider that in our trial design.

Of course, the patient's preferences, risk tolerance, and safety are always the highest priority. Side effects are also a prime consideration. The neoadjuvant component can weaken the patient before surgery. We have seen some resistance among surgeons for that reason. Clearly, it is incumbent upon us to help the patient understand all the options and the potential risks and benefits and to work with surgeons to address these issues.

But with the possibility that the sarcoma has shrunk before surgery and might then be resectable, this approach can be the right path if there is evidence that the cancer will not recur. Data is emerging from clinical trials, even in NSCLC, where people are having open-chest surgery to remove a tumor.

Strong early evidence of improved outcomes

At this point, we are in the very early stages of trials using neoadjuvant therapy for NSCLC, head and neck, and gastrointestinal tumors and will need at least 10 years to gauge longer-term survival rates. But we do have strong evidence that five years after these treatments, more patients become resectable and have better chances for survival.

Parexel is leading the way in innovative study designs in oncology, working closely with drug developers on flexible approaches to trial design. We have extensive experience with neoadjuvant therapy in breast cancer and are currently conducting trials targeting NSCLC. We are encouraged by the collaboration of many stakeholders in finding ways to speed new treatments to patients who await them.

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