Advancing Synovial Sarcoma Treatment With ADP-A2M4

BY BRIAN VAN TINE, MD, PHD

I am one of the investigators in the phase I, open-label, dose-escalation trial with ADP-A2M4 designed to evaluate the safety, tolerability, and anti-tumor activity in certain patients with solid tumors. At the recent European Society for Medical Oncology (ESMO) Congress, I presented updated findings from 12 patients with synovial sarcoma, which demonstrated that ADP-A2M4, a T-cell therapy targeting the MAGE-A4 antigen, had a clinical response rate of 58 percent. As synovial sarcoma is one of the rarest types of cancers with limited response rate of 58 percent. As synovial sarcoma is one of the rarest types of cancers with limited treatment options, this research is very meaningful for patients battling the deadly cancer.

Road to Sarcoma Treatment
Synovial sarcoma is a soft tissue sarcoma, which represents less than 1 percent of all malignant

TAILORx Update: Refinement of Risk & Benefit

BY SHANNON PUHALLA, MD, PRIYA RASTOGI, MD, ELEFHERIOS MAMOUNAS, MD, MPH, FACS, & NORMAN WOLMARK, MD

Based on robust retrospective analyses from randomized clinical trials and large patient cohorts, the use of genomic assays that determine risk of recurrence and estimate potential benefit of adjuvant chemotherapy are commonplace to determine treatment of early-stage breast cancer. The Oncotype Dx recurrence score (RS) is the test most commonly used in the U.S.

Last year, data from the primary analysis of the landmark prospective Trial Assigning Individualized Options for Treatment (TAILORx), which randomized patients with node-negative disease and a recurrence score of 11-25 to endocrine therapy alone or to chemotherapy and endocrine therapy, were published (N Engl J Med 2018;379:111-121). For the entire study population, there was no significant benefit to the administration of chemotherapy in those with intermediate RS. Subset analyses suggested, however, that there was a possibility of chemotherapy benefit in women who were < 50 years old with a RS of 16-25.

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Chemotherapy Can Set the Stage for Drug-Resistant Leukemia at Relapse

Chemotherapy has helped make the most common childhood cancer one of the most curable, but researchers have evidence that the treatment may also prime some patients for relapse. Results published in the journal Blood reported that treatment-induced mutations cause drug resistance in some patients whose acute lymphoblastic leukemia (ALL) returns (2019; doi: 10.1182/blood.2019002220).

“Our study reveals the evolution dynamics of pediatric ALL, which suggest for the first time that chemotherapy treatment, particularly thiopurines, can cause mutations that lead to drug resistance in patients,” said study co-corresponding author Jinghui Zhang, PhD, Chair of the St. Jude Children’s Research Hospital Department of Computational Biology.

The study involved 103 young ALL patients who relapsed. Most relapsed 9 or more months after diagnosis. The analysis revealed that about 20 percent of these patients had treatment-related mutations at relapse, some associated with drug resistance.

“The mutational signatures are specific and therapy-related, as they are only present in the genomes of relapsed ALL patients but not in other pediatric or adult cancer genomes,” Zhang noted. The findings underscore the need for less toxic therapies and precision medicine approaches, said co-corresponding author Ching-Hon Pui, MD, Chair of the St. Jude Department of Oncology.

Candidates in development include immunotherapies such as CAR T cells and bispecific antibodies.

“This study points to the potential need to individualize therapy when...
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Recent additional analysis from the TAILORx dataset (N Engl J Med 2019;380:2395-2405; JAMA Oncology 2019; doi.org/10.1001/jamaoncol.2019.4794) examined the added effect of clinical risk on patient outcomes with known genomic risk. This pre-planned subset analysis aimed to determine how clinical risk added to genomic risk in terms of prognosis and prediction of chemotherapy benefit. Further, the potential association with age and menopausal status was explored.

When the TAILORx trial was developed, the Adjuvant! Online program was often used to calculate breast cancer risk and estimate potential benefit from adjuvant endocrine therapy and adjuvant chemotherapy. This program was developed based on SEER and EBCCTG data. For many years now, this tool has not been available and, therefore, TAILORx investigators used a clinical risk algorithm similar to the one employed in the recent MINDACT prospective validation of the 70-gene MammaPrint assay (N Engl J Med 2016;375:717-729). Low clinical risk was set as a tumor ≤ 3 cm with low histologic grade, ≤ 2 cm with intermediate histologic grade, and ≤ 1 cm with high histologic grade. High clinical risk was any tumor that did not meet those characteristics. There was clinical risk information available for nearly all patients (9427 patients, 97%) with 70.2 percent falling into low clinical risk and 29.8 percent having high clinical risk. About two-thirds of the patients were > 50 years of age. The majority of women who were premenopausal received tamoxifen (78%) with 35 percent later switching to an aromatase inhibitor (AI) and the majority of women who were postmenopausal received an AI (70%).

As expected, clinical risk was prognostic for recurrence. There was a higher risk of distant recurrence in patients with high clinical risk compared to those with low clinical risk regardless of age, recurrence score, or type of therapy received. Furthermore, a model combining clinical and genomic risk was statistically significant in terms of predicting invasive disease-free survival. The hazard ratio for high versus low clinical risk was 2.42 (P<0.001). When the recurrence score was examined as a continuous variable, for each point increase in RS the hazard ratio was 1.08 (P < 0.001).

For women > 50 and RS 11-25, the overall risk of recurrence was low. The rate of distant recurrence was 3-4 percent with low clinical risk and higher (8-9%) with high clinical risk. These outcomes did not change if chemotherapy was given or not. For women < 50 with RS 11-25 and low clinical risk, rates of distant recurrence were similar whether chemotherapy was given or not (3.9% with and 4.7% without). However, for those with RS 11-25 and high clinical risk the risk of distant recurrence was 6.1 percent with chemotherapy but 12.3 percent without. Clinical risk was not associated with distant recurrence in the low-risk cohort of patients (RS < 11) treated with endocrine therapy only (< 1.8% risk regardless of clinical risk). However, clinical risk was important in the high RS cohort (RS >26) where all women received chemotherapy. In those with high clinical risk, the risk of distant recurrence was 19.8 percent in patients ≥ 50 years and 13.3 percent in those < 50; whereas with low clinical risk, it was 7.0 percent in patients ≥ 50 years, and 6.2 percent in those < 50 years.

In contrast, clinical risk did not predict chemotherapy benefit, regardless of age. As seen, however, in the original TAILORx publication, there was a trend towards chemo benefit if age < 50, especially if the RS was 21-25, but this was irrespective of clinical risk. Incorporating clinical risk did not add further to the prediction of chemotherapy benefit in these women (age < 50, RS 21-25) with low clinical risk women having an absolute chemotherapy benefit of 6.4 ± 4.9 percent and high clinical risk women having a benefit of 8.7 ± 6.2 percent. In women with RS of 16-20 and high clinical risk, the benefit to chemotherapy was 6.3 percent ± 4.9 percent. In contrast, if the clinical risk was low with RS 16-20 and age <50, there was no benefit to chemotherapy (-0.2 ± 2.1%). This suggests that there may be some validity to incorporate clinical risk in the treatment decision-making in the < 50, RS 16-20 population.

Chemotherapy benefit was evident in women 41-45 years of age and in those 46-50 years who were premenopausal, but there appeared to be no benefit in women < 40 years of age or in those 46-50 who were postmenopausal.

The potential for chemotherapy benefit to be a function of castration effects was further explored in those women < 50 with RS of 16-25. Chemotherapy benefit was evident in women 41-45 years of age and in those 46-50 who were premenopausal, but there appeared to be no benefit in women < 40 years of age or in those 46-50 who were postmenopausal. This suggests that chemotherapy benefit may in part (or as a whole) be the result of induction of permanent ovarian suppression from chemotherapy, as older premenopausal women are more likely to stay in menopause after adjuvant chemotherapy and younger women are more likely to recover ovarian function. It is important, however, to acknowledge that these findings of chemotherapy benefit in women < 50 by RS, age, and menopausal status, while certainly thought-provoking and scientifically valid, are based on an unplanned exploratory subset analysis.

This recent TAILORx update illustrates the intersection between genomic and clinical data. In this group of patients with relatively good overall prognosis (i.e., ER-positive and node-negative), there is heterogeneity in outcomes. Both clinical features and RS can be used to identify patients with higher versus lower risk of recurrence. The ongoing contribution of the RS over that of clinical risk in prediction of chemotherapy benefit, whether due to cytotoxic or ovarian suppressive effects, continues to be clinically relevant and useful. The results further demonstrate that there is still considerable room for improvement in outcomes in those patients with high RS and high clinical risk. This group of patients has risk of recurrence (close to 20%) despite the receipt of chemotherapy and endocrine therapy, making such patients good candidates for future clinical trials testing novel agents.

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