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Multi-platform molecular profiling: A precision medicine victory built on cytotoxic chemotherapy

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In this issue of *The Cancer Journal*, Seeber et al present their findings applying precision medicine methodologies to a very difficult population: patients with persistent cancer who have already received multiple therapies. These are patients turning to precision medicine often as a last resort, and yet progression free survival was significantly increased compared to prior therapy. This compelling study is a retrospective pooled analysis of multi-platform molecular profiling (MMP); an approach utilizing a combination of precision medicine diagnostics: next generation sequencing, immunohistochemistry, and in-situ hybridization. The study ultimately reports MMP to be a beneficial for patient outcome through the selection of targeted therapies, with the majority of decisions “driven by immunohistochemistry data with predictive associations for cytotoxic treatments.”

Studies like this one demonstrate the pace at which precision diagnostics are evolving. The patients’ tumors in this study underwent a range of tests that capture the changing technology, from immunohistochemistry to diagnostic Sanger sequencing to 46 and 592 gene panels and full exon coverage. This study includes pooled-analysis data from four studies that employed MMP, defined as “a characterization of tumors on the genetic and protein level.” In the ONCO-T-Profile project, 110 patients with solid tumors and no standard treatment available underwent targeted therapies selected by treating physicians as well as an expert panel. Next, a multicenter pilot study of 28 refractory breast cancer patients (Side-Out) underwent treatments selected by a team of oncologists and pathologists. This group provided the most structured system of treatment, with preference for multimodal instead of single agent therapy. Two additional cohorts of refractory solid tumor patients underwent MMP profiling in Lebanon (62 patients) and Australia (54 patients) and had treatment determined by more traditional discussion at tumor boards. Of the 202 enrolled and profiled patients between the four groups, 166 were able to be evaluated and survived to receive treatment based on their molecular profile. Interestingly, more than 80% of those 166 were treated with cytotoxic chemotherapy alone. Of the 140 patients with comparison of prior non-profile based treatment, 71% received chemotherapy alone, 8% chemo and targeted therapy, 9% targeted therapy alone, and the rest a combination with hormone therapy.

The authors found that the MMP-based approach had a clinical benefit for 52% of patients, with 180 days of median progression free survival (PFS) vs. 62 days on their prior treatment.

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For those helped by MMP and with no other standard therapies available, there was a median of 4 months added PFS. The authors note that progression free survival appeared longer with targeted therapy than chemotherapy based regimens alone, but that many patients were helped by the integration of biomarkers predication response to conventional chemotherapy. As the authors point out, the results are limited by the use of four studies with slightly different approaches to MMP, the need for open label design, and its exclusion of patients with a life expectancy of three months or less.

A number of recent studies have demonstrated the benefit of therapy targeted to patient-specific tumor diagnostics. A recent meta-analysis of 570 studies (32,149 patients) showed a benefit of phase 2 personalized targeted therapies compared to non-personalized targeted therapies and cytotoxic chemotherapy alone, in terms of better outcomes and fewer deaths.¹ Additionally, a meta-analysis of stage 1 oncology studies demonstrated that strategies using biomarkers to target therapy were more effective than use of “targeted” therapies used without biomarkers, in terms of increased treatment response (median, 30.6% vs 4.9%) and progression-free survival (median, 5.7 vs 2.95 months). These improvement have been built on the of large successes of pathway-specific targeted agents in the last few decades, including the human epidermal growth factor receptor 2 antibody trastuzumab in breast cancer², the BCR-ABL inhibitor imatinib for CML³ and the BRAF inhibitors vemurafenib⁴ and dabrafenib⁵ in melanoma.

While these selected “home runs” of targeted therapies are compelling, there have been numerous important “base hits” demonstrating predictive associations of certain tumor-specific biomarkers with traditional cytotoxic chemotherapies. This study yields great benefit to our understanding of the effects of targeting therapy, with the added utility of demonstrating that a targeted approach isn’t just a hunt for newer and better pathway-specific “silver bullets.” Instead, studies like the one demonstrate that we should not be so quick to abandon some of our more established cytotoxic agents, even in a treatment-resistant patients, when there is predictive associations between tumor diagnostics and cytotoxic treatments.

It is our belief that precision medicine approaches will continue to build base hits and home runs in terms of patients’ outcomes. For patients with high-risk and refractory cancer, to continue to use “established” therapies without taking into account tumor biology will often not be enough.

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