Clinics in Oncology

Review Article
Published: 23 Nov, 2017

Predictive Markers of Efficacy

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Abstract

Cancer treatments have long relied on predictive markers of efficacy. Once a chemotherapy drug or regimen is shown to be efficacious for a particular tumor type, that becomes the predictive marker of efficacy. Hormone receptor positivity of breast cancer remains the predictive marker for responsive to anti-estrogen receptor therapy.

We have now entered firmly into the age of precision cancer therapy. Next generation sequencing (NGS) of solid tumors or liquid biopsies (cell-free DNA) has taken the use of predictive markers of efficacy a step further by attempting to identify so-called actionable molecular abnormalities that are beginning to replace the tissue of origin as the primary consideration in helping patients choose therapies for many examples of metastatic cancer.

Ideally, clinical studies are completed where eligible patients have tumors characterized by the presumptive predictive marker and demonstrate improved efficacy in those patients receiving the targeting therapy versus those not receiving the targeting therapy. Without clinical trials that specifically address the benefit or lack of benefit for a particular therapy, redefining the definition of a predictive marker can be problematic. In this article, examples of predictive markers of efficacy now routinely relied upon in advising patients with lung cancer, colon cancer and breast cancer are used to illustrate the challenges involved in choosing and later redefining predictive markers of efficacy.

Identifying Surrogates of Efficacy

Identifying markers that predict efficacy has become key to the success of many standard cancer treatments. The use of the targeting agentsgefitinib and erlotinib in the treatment of non-small-cell lung cancer (NSCLC) years ago underscored the importance of identifying a predictive marker of efficacy. Originally shown to have only very limited efficacy in the treatment of NSCLC, either is now considered a preferred first line therapy for EGFR-mutated NSCLC. The drugs are primarily EGFR tyrosine kinase inhibitors. Given the central dogma of biology, one would expect candidates as a predictive marker of efficacy to be wild type EGFR amplification, normal EGFR over expression, a somatic EGFR oncogene, or expression of oncogenic EGFR protein product. Because the drug acts on the expressed product, one would further assume that of the possible predictive markers for efficacy, EGFR protein expression would be most valuable. However, these inhibitors are far more effective in inhibiting oncogenic products of somatically mutated EGFR. As a result, efficacy is overwhelmingly limited to patients with NSCLCs that demonstrate certain precise driver somatic EGFR mutations. Large randomized studies predict great benefit from these tyrosine kinase inhibitors when the predictive marker for efficacy is one of those somatic EGFR mutations in the tumors (egerlotinib, gefitinib) [1,2].

Since most targeting agents target over-expressed proteins or oncoproteins, protein expression defining the predictive marker of efficacy often involves protein expression assays. For example, if a NSCLC demonstrates PD-L1 protein expression in 50% of the cancer cells, the PD-1/PD-L1 inhibitor pembrolizumabis endorsed as standard first line therapy for metastatic NSCLC because demonstrating this feature has been shown to result in a survival benefit with the use of this drug [3,4]. Also, the authors of the National Comprehensive Cancer Network (NCCN) guideline do state that "patients with PD-L1 expression just below and just above 50% will probably have similar responses" [5]. In so doing, they are saying that it is a reasonable extrapolation to expect that patients with such tumors might similarly benefit.

The presumed mechanism of action of the targeting therapy may be largely irrelevant as long as the results of the clinical trial confirm the predictive value of the predictive marker. This principle is illustrated in the case of PD-L1 inhibitor use and deficient mismatch repair (dMMR) gene expression in colorectal cancers, where the response rate for dMMR colorectal cancers to treatment with PD-L1

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Received Date: *19 Sep 2017*
Accepted Date: *16 Nov 2017*
Published Date: *23 Nov 2017*

Citation:
Sorscher S. Predictive Markers of Efficacy. Clin Oncol. 2017; 2: 1374.

inhibition is roughly 40% compared to essentially no responses with proficient MMR (pMMR) expression [6].

Predictive markers may also be crucial in predicting a lack of responsiveness to targeting drugs. For example, while anti- EGFR antibody therapy (egscetuximab, panitumumab) improves the standard therapeutic efficacy for metastatic colorectal cancer, it has no beneficial effect if the tumor harbors a KRAS or NRAS mutation. Again, the critical finding was the clinical data that statistically clearly confirmed a lack of efficacy for these agents in that setting [7-9].

HER2 gene amplification and/or over expression of HER2 protein in breast cancer as a predictor of efficacy with the use of trastuzumab is a key and robust example of modern clinical precision oncology. The efficacy for the use of trastuzumab combined with chemotherapy compared to chemotherapy alone for prolonging survival or reducing the likelihood of recurrence after surgery (roughly a 40% relative risk reduction) was remarkable. The 2007 expert ASCO/CAP panel appropriately recommended that basically the same eligibility criteria for defining a tumor as HER2-positive in the adjuvant trials be used as the predictive marker for endorsingtrastuzumab'suse [10].

However, as was the recent case with the PD-L1 expressing NSCLCs described above, the results with trastuzumb's use were so robust and toxicities so modest that in 2013 the ASCO/CAP expert panel expanded the definition of HER2-positive cancer to include such measures as identifying HER2 gene amplification using alternative probe FISH assays and identification of polysomy for chromosome 17. The authors acknowledged that clinical data supporting their expansion to include patients with tumors that in 2007 would have been defined as HER2-negative was supported by very little clinical data. The 2013 panel concluded that their decisions to expand the defining criteria were made so that "the right patient receives the right treatment [11]."

Unfortunately, in expanding the definition of HER2-positive disease, the 2013 expert ASCO/CAP guideline veered from the fundamental principles for identifying predictive markers of efficacy. For example, expanding the definition of HER2-positivity to include tumors demonstrating polysomy might be considered endorsing an unproven surrogate of a proven predictive marker. In contrast to the cases of EGFR kinaseinhibitors (in lung cancer) and anti-EGFR antibodies (in colorectal cancer), there were no large bodies of clinical data to rely on to determine whether patients with breast cancers defined as HER2-positive by the new definitions benefitted from anti-HER2 therapy.

Also, it seemed naïve to think that patients would be willing to be randomized to confirmatory trials involving highly effective anti-HER2 therapy (defined by 2007 definitions of HER2-positivity) versus no such therapy, when their third party payers would already be willing to approve the drugs based on the 2013 ASCO/CAP recommendation, particularly after the subsequent NCCN endorsement of those recommendations.

Finally, while it seemed safe to endorse these relatively non-toxic anti-HER2 drugs with limited clinical results to support their use in patients who only met the 2013 definitions, the treatment landscape has changed for HER2-negative metastatic disease with the introduction and FDA approval of CDK4/6 inhibitors. Relatively well-tolerated and oral, CDK 4/6 inhibitors in combination with aromatase inhibitors result in a roughly 55% response rate as first line metastatic disease therapy, although their use is currently limited to patients whose tumors are HER2-negative [12]. This left open the question of whether patients with metastatic breast cancer whose tumors met the 2013 definition of having HER2-positive disease (but not the 2007 definition) should receive CDK4/6 inhibitors, anti-HER2 therapy or, at least at some point, both.

Heraclitus wrote "no man can stand in the same river twice," since the river changes and the man changes. Another interpretation of his wisdom is that an opportunity lost may be lost forever. The breast cancer guidelines are expected to be updated and likely changed soon. In spite of more than 20 years of anti-HER2 therapies which have benefitted hundreds of thousands of woman, the original definition of the surrogate marker for efficacy continues to hinder reliable determination of which patients with tumors deemed HER2-positive by expanded definitions will benefit from these remarkable drugs.

Conclusions

During the 1990's, the predictive marker for recommending stem cell or bone marrow transplant for many women with metastatic breast cancer was almost as simple as having breast cancer. In fact, breast cancer was the most common indication for such transplants. It is now clear that designing clinical studies with thoughtful consideration of the predictive markers to be studied in these trials is fundamental to improving the outlook for our patients.

Paradoxically, in terms of clinical outcome from a treatment, the mechanism of action of the drug-and even the tissue of origin or molecular abnormalities of the tumor-are overshadowed by identifying a marker that predicts benefit.

Once a clinical trial demonstrates efficacy for a targeting agent, expansion of the definition of the "positive" predictive marker of efficacy used in that trial by showing concordance using other assays for the same metric, lowering the threshold for defining the patient's tumor as "positive" or by identifying a surrogate for the predictive marker (egpolysomy as surrogate for protein over expression) all present uncertainty. The best remedy is to conduct clinical trials specifically involving patients with tumors characterized by the proposed new definition.

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