The Wave of the Future:
Genetic Profiling in Treatment Selection

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Chemotherapy treatment recommendations traditionally have been based on the anatomic site of origin and the histology of the tumor. More recently, treatment options are transitioning to targeted therapies, in which drug selection is based on mutations present in an individual tumor. Genomic testing is a developing area that involves testing tumors to determine their molecular or genetic characteristics, then matching those characteristics to treatments that specifically target them.

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Presenting with a palpable chest mass and large symptomatic pleural effusion, J.P., an 84-year-old woman, was diagnosed with a locally advanced, unresectable histiocytic sarcoma of the lung, which had eroded into the chest wall. A thoracentesis was completed with negative cytology. Staging studies did not reveal any distant metastases. Genomic profiling testing then was ordered on the original tumor sample. Prior to her diagnosis, J.P. had experienced mild chest pain at the site of her mass, as well as a 10-pound weight loss. She otherwise remained in her usual state of health. J.P.’s prior medical and surgical history included right total knee replacement, tonsillectomy, osteoarthritis, and basal cell carcinoma of the face.

Treatment planning for J.P. commenced. She was seen and evaluated by radiation oncology. Radiation therapy was not recommended at the time, given her absence of symptoms, and she was encouraged to pursue chemotherapy. Two cycles of CVP (cytoxan, vincristine, and prednisone) were given. A clinical examination of J.P.’s chest wall mass after those two cycles led her healthcare providers to believe that the disease had progressed, as evidenced by the increasing size of the mass. Computed tomography (CT) scans were completed to further evaluate the response to chemotherapy; unfortunately, they revealed progression of disease with a new pulmonary nodule, and CVP was discontinued. Through genomic profiling, J.P. was found to have three genomic alterations: \textit{MET}, \textit{TP53}, and \textit{ZMYM3}. Of the three alterations, the \textit{MET} mutation has associated therapies that have been approved by the U.S. Food and Drug Administration (FDA). One such therapy is crizotinib, which has been approved for non-small cell lung cancer, not for histiocytic sarcoma. Given the presence of the \textit{MET} alteration, J.P. was treated with crizotinib.

**Personalized Medicine**

Information gained through clinical trials directs the establishment of national treatment guidelines and treatment recommendations. Chemotherapy regimens have long been based on clinical trials that determine whether a drug is effective at a tumor’s anatomic site of origin. The histology of the tumor and the stage of disease are also considered.

Now, treatment options are transitioning to targeted therapies. This process of matching molecular or genetic alterations to drugs that specifically interfere with them allows the oncology team to personalize treatment, which is based on the genetic characteristics of each tumor. Personalized medicine, or precision medicine, is a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease. In regard to cancer, personalized medicine uses specific information about a person’s tumor to help diagnose him or her, plan treatment, find out how well treatment is working, or make a prognosis.

Genomic testing is an emerging science in oncology, but proven examples of personalized therapies based on genetic alterations are available for review. One of the earliest examples of personalized treatment based on genetic mutations exhibited in tumor cells is the use of trastuzumab in HER2-amplified breast cancer. Additional examples of success include the use of imatinib in Philadelphia chromosome–positive chronic myeloid leukemia and gastrointestinal stromal tumors, erlotinib in epidermal growth factor receptor-mutated non-small cell lung cancer, and vemurafenib in \textit{BRAF}-mutant melanoma (Frampton et al., 2013).

Two of J.P.’s genomic alterations, \textit{TP53} and \textit{ZMYM3}, do not have any FDA-approved therapies associated with them, although the third, \textit{MET}, has FDA-approved therapies in other tumor types. These therapies are cabozantinib and crizotinib. Cabozantinib’s existing indication is for progressive metastatic medullary thyroid cancer, whereas crizotinib is approved for \textit{ALK}-positive, metastatic non-small cell lung cancer. Activated \textit{MET} stimulates a chain of events including “cell motility and scattering,
angiogenesis, proliferation, branching morphogenesis, invasion, and eventual metastasis” (Ma et al., 2008, p. 1025). Crizotinib is a dual MET and ALK kinase inhibitor. Ou et al. (2011) reported activity with the use of crizotinib in non-small cell lung cancers, which were positive for MET. An additional study by Lennerz et al. (2011) further revealed activity with crizotinib while studying gastroesophageal cancers, which were MET amplified.

Genomic testing is on the rise, and multiple genomic profiling tests are now available; J.P. used FoundationOne, a genomic profiling service that relies on next-generation sequencing to identify genetic mutations present in cancer. FoundationOne tests for 315 cancer-related genes, plus select introns. The identification of these genes often has clinical significance that assists in drug selection. Foundation Medicine, Inc., offers two FoundationOne genomic tests, one for solid tumors and another for hematologic malignancies. In clinical patient samples using a version of FoundationOne that analyzed 236 cancer-related genes and introns from 19 genes typically rearranged or altered in cancer, 97% of genes exhibited an alteration, and 85% of samples had at least one clinically relevant alteration that could be targeted with a specific anticancer drug (Foundation Medicine, Inc., n.d.).

Financial Considerations

Cost and reimbursement are of concern to patients undergoing cancer treatment (Stump et al., 2013), and the cost of genetic profiling is significant. The price of a FoundationOne test is $5,800, which is average among testing companies. As with other testing, insurance reimbursement is not guaranteed, and the cost to the patient varies. Most, if not all, testing companies have financial assistance programs, which help patients who have coverage through insurance, as well as patients who are uninsured and underinsured. Although the cost of the test is high, a patient should also consider the cost of cancer treatment. If targeted treatment results in a better outcome for a patient, the benefit is priceless. Targeted therapy could also eliminate the use of other costly therapies, which may not be as effective.

J.P.’s treatment selection was driven by her FoundationOne results. She appears to be improving, with visible reduction in the size of the mass on her chest wall.

Conclusion

It advances from traditional trial-and-error methods of establishing treatment to identifying genetic characteristics of cancer cells, which can be matched to corresponding pharmaceuticals. These characteristics often cross tumor types. Treatments are no longer solely based on anatomical site of origin, as demonstrated in the case of J.P., who was prescribed a traditional lung cancer drug for a histiocytic sarcoma. Genomic profiling is a key component in the detection of these alterations, which are often associated with effective therapies. As this is an evolving area, many questions remain. These genetic alterations, and associated personalized treatments, will likely be gained in the coming years. Much remains unknown. What is known is that innovations that will benefit patients are continuing to be discovered.

References

Foundation Medicine, Inc. (n.d.) FoundationOne® experience on 13,000+ patients. Retrieved from http://www.foundationone.com/docs/FoundationOne%20Experience%202013k+pdf


Timing of the Test

Genomic testing can be done at any time. Ordering testing at the time of diagnosis is recommended, as the results may direct initial treatment. Even if the information is not used for initial treatment, it could provide options for future treatment, particularly in the metastatic setting; tumor genomics will not change. For patients who experience recurrent disease, testing can be ordered on initial biopsy samples. The patient would require an additional biopsy only if the original tumor tissue is not available, or if the quantity of material or the preservation method is not acceptable. If testing is performed through FoundationOne, the sample may be sent as a formalin-fixed, paraffin-embedded block or as 8–10 hematoxylin and eosin slides; this is a standard specimen request, although different testing companies may vary slightly in their requests. Results take about 14–17 days.

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