



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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Key words: genetics; chemotherapy; cancer treatment

Digital Object Identifier: 10.1188/14.CJON.717-718

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: *MET*, *TP53*, and *ZMYM3*. Of the three alterations, the *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 *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 *BRAF*-mutant melanoma (Frampton et al., 2013).

Two of J.P.'s genomic alterations, *TP53* and *ZMYM3*, do not have any FDA-approved therapies associated with them, although the third, *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 *ALK*-positive, metastatic non-small cell lung cancer. Activated *MET* stimulates a chain of events including "cell motility and scattering,