INTRODUCTION

A 63-year-old man is diagnosed with papillary thyroid cancer in July 2014 and undergoes thyroidectomy followed by radioactive iodine ablation. In February 2015, metastatic disease is detected midline at the level of the thyroid isthmus and in the right supraclavicular region and lungs. Histopathologic examination identifies the metastases as anaplastic thyroid cancer (ATC; stage IVc) that has transformed from papillary cancer (Figure 1).

The patient receives two cycles of cisplatin plus adriamycin chemotherapy, but the cancer rapidly progresses. Subsequent treatment with two cycles of paclitaxel is similarly ineffective in halting tumor proliferation. He is referred by his primary oncologist to Indiana University Health Precision Genomics for assessment.

Figure 1. Histopathologic images of papillary and anaplastic thyroid cancer

A: Micrograph of papillary thyroid cancer demonstrating prominent papillae with fibrovascular cores.

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B: Micrograph of ATC showing diffuse, anaplastic cells with enlarged, pleomorphic nuclei, frequent mitosis, and neither papillary nor follicular differentiation. Clinical, pathologic, and experimental evidence support the hypothesis that ATC transforms from pre-existing differentiated thyroid cancer.

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OVERVIEW ANAPLASTIC THYROID CANCER

ATC is a rare form of undifferentiated cancer that accounts for less than two percent of all thyroid cancers but has a disproportionately high mortality rate of 33 to 50 percent. Patients are usually in their sixth or seventh decade of life at presentation, have an average median survival of five months, and fewer than 20 percent are alive one year after diagnosis. ATC has a sudden onset and rapid progression, with only 10 percent of patients presenting with a tumor confined to the thyroid. Forty percent of patients have extra thyroidal extension and lymph node involvement, and the remainder present with distant metastasis (stage IVc*), of which the mediastinum and lung are the most common sites of tumor spread.3

In patients with advanced metastatic ATC, no cytotoxic therapy has been definitively shown to have curative potential or to prolong survival rates.4 These individuals and others with refractory late-stage malignancies may benefit from a precision medicine approach to cancer care.

APPLICATION OF PRECISION MEDICINE IN ONCOLOGY

Systemic cancer treatment is undergoing a paradigm shift, moving away from the primary use of cytotoxic chemotherapy to the application of precision medicine approaches that seek to match genomic aberrations with potential treatment avenues. Cancer is a logical first choice for evaluating and enhancing the impact of precision medicine because: 1) it is a disease of DNA (linked to changes in the genome); 2) a variety of therapies are available that target specific genomic aberrations.

“Cancer is not a single disease, and poor outcomes are the result of a ‘one size fits all’ approach to care,” says Milan Radovich, PhD, co-director of IU Health Precision Genomics and assistant professor of surgery and medical & molecular genetics at IU School of Medicine. “Many cancers have been shown to have targetable pathways that may benefit from the application of precision medicine to tailor therapy based on the uniqueness of the tumor and patient.”

“Affordable and fast high-throughput genomic testing now makes it possible to simultaneously evaluate hundreds, even thousands of driver aberrancies to identify targets that are potentially actionable with drugs already approved by the US Food and Drug Administration (FDA) or available through participation in clinical trials,” Dr. Radovich continues. “These targets may be overlooked in standard clinical practice due to their rarity, novelty, or presence in cancer lineages not normally associated with a particular target.”

MOLECULARLY TARGETED CANCER TREATMENT

Increased understanding of the molecular etiology of cancer has led to the development of two categories of targeted therapy: 1) drugs that identify and home in on overexpressed or mutationally-activated proteins required for the continued survival and growth of malignant cells, and 2) “checkpoint inhibitors” designed to reinvigorate and potentially expand the anticancer response of the immune system.

Research suggests that selecting a targeted agent on the basis of the molecular profile of a patient’s tumor—-independent of tumor location and histology—may be safer and more effective than cytotoxic chemotherapy (Table 1),5,7 as evidenced by the success of:

- Imatinib (Gleevec®) in the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia
- Erlotinib (Tarceva®) in the treatment of epidermal growth factor receptor-mutated non-small cell lung cancer

*Secondary to the extremely aggressive behavior of ATC, the American Joint Committee on Cancer defines all stages as stage IV.2
- **Trastuzumab (Herceptin®)** in the treatment of metastatic HER2-overexpressing breast and gastric cancers
- **Vemurafenib (Zelboraf®)** in the treatment of BRAF-mutant melanoma

**TABLE 1. Proposed benefits of molecularly targeted cancer treatment**

- Improved medical decision-making
- Delivery of appropriate therapies tailored to a patient's genomic sequence variants rather than to that of the general population
- Optimized disease prevention strategies (e.g., lifestyle and behavioral modification) and pharmacoprevention
- Reduced exposure to medications that
  - Are less effective
  - Have the potential for greater toxicity, resulting in a lower incidence of treatment-related complications
- Reduced healthcare costs
- Enhanced patient satisfaction with the therapeutic process, improved tolerance of therapy, and better adherence to treatment

Genomic sequencing is performed on tumor tissue previously collected from the patient and reveals two interesting findings: 1) the presence of the BRAF V600E mutation, a mutation more commonly seen in melanoma, and 2) tumor positivity for the immune marker programmed death-ligand 1 (PD-L1).

**USING GENOMIC SEQUENCING TO INDIVIDUALIZE THE TREATMENT REGIMEN**

Developing a personalized treatment plan involves exploiting tumor-specific vulnerabilities identified through genomic sequencing. The most common DNA mutations and RNA overexpressions identified at IU Health Precision Genomics to date are shown in Table 2.

With regard to the patient described in the case study, two tumor-specific vulnerabilities required consideration:

**BRAF V600 mutations.** BRAF is a protein kinase within the RAS-RAF signaling pathway. BRAF V600 mutations occur in about half of all cutaneous melanomas and have also been identified in nonmelanoma cancers, such as papillary thyroid cancer. These mutations may promote overactive signaling and cell proliferation.

Vemurafenib binds to some forms of mutated BRAF, including V600E, inactivating the oncogenic protein. As a result, downstream proliferation signaling is blocked, potentially leading to apoptosis of cancer cells. In a multicenter phase II clinical trial that enrolled 132 patients with previously treated BRAF V600-mutant metastatic melanoma, vemurafenib induced clinical responses and improved survival in more than half of the patients. A cohort study that included seven patients with ATC found that two patients (29 percent) responded to vemurafenib therapy: one patient had a complete response, the other had a partial response.
**PD-L1 pathway.** The PD-L1 pathway plays a key role in maintaining immune homeostasis by binding to specific receptors on T cells. Such binding downregulates cytotoxic T cell activity, thereby protecting normal cells from autoimmunity. In cancer, the PD-L1 pathway can shield tumors from cytotoxic T cells, ultimately inhibiting the body’s antitumor immune response.

Nivolumab is a monoclonal antibody that blocks PD-L1 expressed by tumors and tumor-infiltrating immune cells, potentially preventing T cell suppression throughout the tumor microenvironment. Nivolumab is approved for the treatment of metastatic squamous non-small cell lung cancer, and phase I/II studies have shown it to have promising activity in patients with advanced melanoma.

**COMBINATION THERAPY**

While the growth of some cancer cells can be impaired by inactivating a single oncogene, tumors may relapse despite pronounced initial responses. Furthermore, some tumors exhibit substantial genomic heterogeneity and fail to respond to single-agent molecular targeting. Combination treatment using drugs that attack the cancer via parallel pathways or that block the same target through different mechanisms allow for greater flexibility in matching drugs to the genetic driver lesions present in each tumor.

TABLE 2. Common DNA mutations and RNA overexpressions identified at IU Health Precision Genomics

**DNA mutations**
- KRAS/HRAS/NRAS
- FGFRs (fibroblast growth factor receptors) and Ligands
- PIK3CA
- Cyclins

**RNA overexpressions**
- MET (hepatocytes growth factor)
- CDH1 (cadherin 1, type 1)
- AREG (amphiregulin)
- EREG (epiregulin)
- VEGFA (vascular endothelial growth factor A)
- hENT1 (human equilibrative nucleoside transporter 1)
- IGF1R (insulin-like growth factor 1 receptor)
- HER2
Genomic recommendations are sent to the primary oncologist (Figure 2). The patient begins treatment with vemurafenib in June 2015, resulting in a mixed response. Nivolumab is added to the therapeutic regimen one month later, and the patient experiences a near-complete response. He continues on combination therapy and is doing well as of November 2015.

Combination treatment using drugs that attack the cancer via parallel pathways or that block the same target through different mechanisms allow for greater flexibility in matching drugs to the genetic driver lesions present in each tumor.

“ACTIONABLE” GENETIC ALTERATIONS

“Approximately 70 percent of genomic testing performed at IU Health reveals a ‘hit,’ meaning that a potentially beneficial cancer drug is identified,” says Dr. Radovich. “While published case reports of exceptional responses to molecular targeted therapy are encouraging, solidifying the utility of cancer genomics in clinical practice requires larger cohorts and clinical trials.”

Several studies are currently underway to provide additional supporting evidence. Noteworthy among them are the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial17 and the American Society of Clinical Oncology Targeted Agent and Profiling Utilization Registry (TAPUR) study.18

NCI-MATCH TRIAL

“The NCI-MATCH trial is analyzing patients’ tumors to identify ‘actionable mutations’ and then assigning treatment based on the detected abnormality,” Dr. Radovich explains. “The goal of the study is to show whether treating cancers according to their molecular aberrations is effective.”

The trial opened for enrollment in August 2015* with 10 arms (additional arms are expected to open in 2016). Each arm will enroll adults ≥18 years with advanced solid tumors and lymphomas that are no longer responding/never responded to standard therapy. The study investigators plan to obtain tumor biopsy specimens from up to 3,000 initial patients. It is anticipated that more than 20 drugs—all approved by the FDA for another cancer indication or being studied in other clinical trials, and all having shown some effectiveness against tumors with a particular genetic alteration(s)—will be evaluated, each in a different study arm.

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*Kathy Miller, MD (317-274-2552) is the principal study investigator at IU Health Melvin and Bren Simon Cancer Center.
TAPUR STUDY

TAPUR is a prospective, non-randomized clinical study examining the anti-tumor activity and toxicity of commercially available, targeted anticancer drugs used for the treatment of advanced solid tumors, multiple myeloma, or B cell non-Hodgkin lymphoma that have a genomic variant known to be a drug target or to predict sensitivity to a drug. The study will initially be launched at sites in Michigan and in North and South Carolina, with the goal of expanding nationally.

Additionally, various pharmaceutical companies, including Novartis and Genentech Roche, are funding “basket clinical trials” in which treatment is based on a genomic target, not a specific type of cancer.

“NON-ACTIONABLE” GENETIC ALTERATIONS

“For about 30 percent of our cancer patients, genomic testing reveals genetic changes that cannot be treated with any currently available drug,” Dr. Radovich reports. “In this situation, the IU Health multidisciplinary tumor board may recommend participation in an early phase clinical trial of a new treatment that may not have an associated genomic biomarker but may have potential anti-tumor activity.”

IU HEALTH TRIAL OF GENOMICALLY-DIRECTED TREATMENT FOR PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER

Triple-negative breast cancer (TNBC), which does not express the genes for estrogen receptor, progesterone receptor, or HER2, accounts for 10 to 20 percent of all invasive breast cancers. The current standard of care is neoadjuvant chemotherapy plus surgery, and approximately 30 percent of patients have a complete pathologic response to treatment. Those with significant postoperative residual disease do poorly, however, and no FDA-approved therapy is available for this patient population. Consequently, the vast majority of these individuals relapse and succumb to their disease within three years, according to Dr. Radovich.

With the hope of improving the prognosis for patients with residual TNBC following standard therapy, IU Health Simon Cancer Center has launched a phase II randomized, controlled trial of genomically-directed therapy (GDT). After undergoing genomic testing, patients are randomized to GDT or their physician’s treatment of choice (i.e., chemotherapy, radiotherapy, watchful waiting). The primary study endpoint is disease-free survival at one and two years.

This first-of-its-kind, proof-of-concept trial is open to enrollment at IU Health and 14 other sites in Indiana. The targeted recruitment is 150 patients, and the results are expected in by 2018.

In January of this year, IU Health opened our first community Precision Genomics service at IU Health Ball Memorial Hospital in Muncie, and will open a second planned site by the end of 2016.

To refer a patient to IU Health Precision Genomics, contact nurse coordinator Stacy Nance, RN at 317.432.0372 or at snance@iuhealth.org.

“The goal of the study is to show whether treating cancers according to their molecular aberrations is effective.”

Milan Radovich, PhD.
SOURCES


IU HEALTH BUSINESS SOLUTIONS PROFILE

Indiana University Health Business Solutions is a division of Indiana University Health—one of the most highly regarded health systems in the nation. Dedicated to helping organizations keep their employees healthy now and in the future, IU Health Business Solutions provides a comprehensive portfolio of services, including On-site Health, Wellness and Health Management, Occupational Health, Executive Health, Employee Assistance and Health Plans. IU Health Business Solutions works with employers to make them stronger, while helping to streamline the delivery of healthcare benefits.

Cancer Centers