

Emerging Role of Genomic Profiling of Advanced Tumors to Aid in Treatment Selection: What Nurses Should Know

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Abstract

Emerging Role of Genomic Profiling of Advanced Tumors to Aid in Treatment Selection – What Nurses Should Know

Objective:

- Explain the role of a new genomic assay (Target Now™) in guiding oncology treatment plans.
- Describe the Target Now™ assay.
- Present a case study where Target Now™ was instrumental in the patient's treatment plan.

Significance and Background

- Predicting effective treatments with chemotherapy or targeted agents for our patients with advanced disease or rare tumors is a common but difficult clinical problem. Target Now™ is a molecular profiling test which analyses the genetic and molecular changes unique to each person's tumor. The test results predict which treatments are likely to be effective or ineffective for the individual patient.

Interventions:

- **CASE STUDY:** A 52 year old female developed progressive metastatic leiomyosarcoma arising from a retroperitoneal primary following surgery. She was treated for recurrent disease with several standard chemotherapy regimens. She had an excellent performance status and requested further therapy for pulmonary and hepatic metastasis. There were no available Phase 1 studies. A biopsy of a metastatic lesion was submitted for Target Now™ assay. Results reported several agents that were predicted not to be of benefit and identified others which could have benefit. This allowed for a choice of temozolomide –an agent not normally used to treat sarcoma. She has tolerated this oral non-toxic agent well with stabilization of her disease.

Evaluation:

- We have seen several patients who were heavily treated or had unusual tumors for whom Target Now™ provided information regarding treatment that may or may not be beneficial.

Discussion:

- Genomic profiling of tumors is the first step toward achieving “personalized medicine” in the care of oncology patients. Nurses should be aware of the utility of this and other assays in the current approaches to patient care.

Background

- Predicting effective treatments with chemotherapy or targeted agents for our patients with advanced disease or rare tumors is a common but difficult clinical problem.
- Unique biomarkers in a tumor provide opportunity for individualized therapy.
- Markers may be identified by FISH, DNA Sequencing, Microarray analysis, IHC PCR and other techniques.
- Target Now™ is a molecular profiling test which analyses the genetic and molecular changes unique to each person's tumor.
- The test results predict which treatments are likely to be effective or ineffective for the individual patient by comparing test results with published clinical literature.

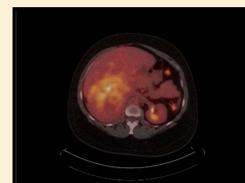
Patient Presentation

CASE STUDY: A 52 year old female presented with flank pain. CT scan showed a 20cm mass around the adrenal.

CT Scan

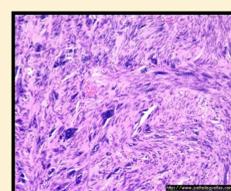


PET Scan



She underwent extensive surgical resection of a retroperitoneal leiomyosarcoma in Jan.,2008. Tumor was Grade 2; T2b,N0,M0 with close surgical margins. She received post-op radiation therapy.

Leiomyosarcoma



Leiomyosarcomas are rare mesenchymal tumors derived from smooth muscle cells. Higher grade tumors tend to relapse and metastasize to lungs.

Patient Course

She remained well until Jan., 2009 when CT scan showed pulmonary and liver metastases (biopsied).

Systemic Therapy

- She was treated with MAI chemotherapy (Mesna, Adriamycin and Ifosfamide) X 4 months.
- Treatment switched to Gemcitabine and Docetaxel with good response for 14 months.
- Disease progressed and treatment was switched to Sorafenib (Nexavar) with stabilization for 12 months.
- Patient was found to be ineligible for Phase 1 Clinical Trial because of a low GFR.

What Therapy Should Be Offered Now?

- Patient had excellent performance status.
- She requested further therapy for pulmonary and hepatic metastases.

TARGET NOW™ SUMMARY - AGENTS ASSOCIATED WITH CLINICAL BENEFIT				
Agents Associated With CLINICAL BENEFIT	Biomarker	Result	Method	Summary Statement
gemcitabine	RRM2	Under Expressed	Microarray-Fluorescence	Low expression of RRM1 and RRM2 has been associated with benefit from gemcitabine.
	RRM1	Negative	IHC	
flourouracil	TS	Negative	IHC	Low expression of TS has been associated with benefit from fluoropyrimidines.
	PTEN	Below Threshold	IHC	
erlotinib, gefitinib	KRAS	Wild type genotype	Molecular	Although EGFR FISH is negative, patients with wild-type KRAS may benefit from EGFR-targeted tyrosine kinase inhibitors.
	EGFR	Negative	FISH	
cisplatin, carboplatin, oxaliplatin	ERCC1	Negative	IHC	Low expression of ERCC1 has been associated with benefit from platinum analogs.
	MGMT	Negative	IHC	
temozolomide	EGFR	Negative	FISH	Low expression of MGMT has been associated with benefit from temozolomide.
	PTEN	Below Threshold	IHC	
cetuximab, panitumumab	KRAS	Wild type genotype	Molecular	Although EGFR FISH is negative, patients with wild-type KRAS may benefit from EGFR-targeted antibodies.

Target Now Assay Report

A biopsy of a metastatic lesion was submitted to Caris Life Sciences (Phoenix, AZ) for Target Now™ assay. Results were available within two weeks and are shown.

Discussion

Results reported several agents that were predicted not to be of benefit and included others which could have benefit. This allowed for a choice of temozolomide – an agent not normally used to treat sarcoma. She has tolerated this oral non-toxic agent well with stabilization of her disease.

Progressive multiple lung metastasesZ



- There were no available Phase 1 studies.
- A biopsy of a metastatic lesion was submitted for Target Now™ assay.

TARGET NOW™ SUMMARY - Agents Associated with LACK OF CLINICAL BENEFIT				
Agents Associated With LACK OF CLINICAL BENEFIT	Biomarker	Result	Method	Summary Statement
irinotecan	TOPO1	Negative	IHC	Low expression of TOPO1 has been associated with lack of benefit from irinotecan.
	Her2/Neu	Negative	IHC	
lapatinib	Her2/Neu	Negative	IHC	Low expression of HER2 has been associated with lack of benefit from HER2 targeted protein kinase inhibitor.
	PTEN	Below Threshold	IHC	
trastuzumab	Her2/Neu	Negative	IHC	Low expression of HER2 has been associated with lack of benefit from HER2 targeted antibody.
	TOP2A	Negative	IHC	
doxorubicin, liposomal-doxorubicin, epirubicin	TOP2A	Negative	IHC	Low expression of TOPO2A has been associated with lack of benefit from anthracycline-based therapy.

Caris Target Now Final Report

Clinical History
Per the submitted surgical pathology report, the patient is a 52 year-old female with a history of leiomyosarcoma.

Pathologic Diagnosis
Soft tissue, retroperitoneal, resection: Leiomyosarcoma, grade 2.

Agents Associated With CLINICAL BENEFIT

ON NCCN COMPENDIUM™

gemcitabine

temozolomide

OFF NCCN COMPENDIUM™

flourouracil

erlotinib, gefitinib

cisplatin, carboplatin, oxaliplatin

cetuximab, panitumumab

Agents Associated With LACK OF CLINICAL BENEFIT

irinotecan

lapatinib

trastuzumab

doxorubicin, liposomal-doxorubicin, epirubicin

Some Examples of Other Genomic Tests

TUMOR TYPE	TEST	THERAPY
Breast	Oncotype Dx®	Hormone +/- Chemotherapy
Colon	EGFR and Kras Mutations	Cetuximab(Erbitux™)
Melanoma	Braf Mutations	Vemurafenib (Zelboraf™)
Lung	EGFR mutations; EML4-ALK	Cetuximab;Crizotinib
Breast	HER-2 neu FISH and IHC	Trastuzumab (Herceptin)

Conclusions

- The tests shown above predict response of an established treatment for a particular tumor type.
- Target Now™ predicts response or resistance to therapies not necessarily established for the tumor tested.
- Both approaches are examples of steps toward achieving “personalized medicine” in the care of oncology patients.
- Nurses should be aware of the utility of these and other assays in the current approaches to patient care.

References

- Von Hoff,D. et al. Pilot Study Using Molecular Profiling of Patient's Tumors to Find Potential Targets and Select Treatments for Their Refractory Cancers. J Clin Oncology. 20:28(33): 4877-83. Epub 2010 Oct. 4.
- Doroshow,J.H. Selecting Systemic Cancer Therapy One Patient at a Time: Is There a Role for Molecular Profiling of Individual Patients With Advanced Solid Tumors? J Clin Oncology 20:28(33): 4869-4871.