Molecular Profiling of Metastatic Breast Cancer in Body Cavity Fluids

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Abstract

Background: The diagnosis of malignant effusion signifies disease progression and is associated with a worse prognosis regardless of tumor origin. The cancer cells in fluids have unique genotypic and phenotypic characteristics that are uniquely different from the primary tumor. Therapeutic guidance should be based on the evaluation of tumor cells in effusions. This study reports the feasibility of molecular profiling for breast cancer metastasis in pleural and peritoneal fluids.

Methods: A computer search was conducted to retrospectively identify malignant fluid samples or cell blocks for molecular profiling. A cell-block was either prepared or available for testing for all samples. An H&E slide was prepared from the cell- block and reviewed by a pathologist before any testing. Malignant cell percentages were determined for purpose of DNA microarray analysis and Sequencing. Appropriate clusters and malignant cells were marked for FISH. The results were reviewed and data compiled to calculate the yield of various molecular predictive tests.

Results: We studied 172 fluid of which 28 were metastatic breast cancer (16.2%). Of the 28 breast cases, 10 IHC biomarkers could be performed in 20 (71.4 %), 1-9 in 1 (3.5 %), while 7 (25%) were insufficient. DNA microarray analysis was done in 10 (35.7%), FISH for EGFR 7 (25%), Her2 Neu FISH 11(39%), cMYC FISH 5 (17.8%) and TOPO2a by FISH 3 (10.7%). Combined IHC/FISH/MA data was available in 10, IHC and FISH data in 11 and IHC and MA data in 10 cases. Combined results of predictive markers provided information on therapeutic guidance in 21 of 28 cases.

Conclusion: Molecular profiling of malignant fluids offers additional opportunities for testing those patients where other tissue samples such as needle core biopsy or resection samples are not available. Molecular profiling provides insight into the molecular characteristics of malignant cells in body cavity fluids and associated expression of unique therapeutic targets.

Background

The diagnosis of a malignant effusion in the serosal cavities is a frequent event in the clinical setting of cancer and usually signifies a worse prognosis. Breast adenocarcinoma is one of the most common tumors, along with ovarian adenocarcinoma, that produces malignant effusions in women. Metastatic cancer cells may have unique characteristics that give them the ability to migrate from the primary tumor, survive in the circulation and invade distant tissues. That is why analyzing these cells is important to create appropriate targeted therapies against those specific subset of cells.

One growing field, not only for the treatment of breast cancer, but for the treatment of all solid tumor is target therapies for cancer. The Caris Target Now™ is proprietary evidence based molecular profiling system for solid tumors providing specific and individualized molecular profiles for guidance of therapy in advanced stages and metastatic malignancies.

Since cancer patients with malignant fluids might be in critical conditions and obtaining a tissue sample for the metastatic nodule might no be feasible, the analysis of the malignant fluid can be the only tissue sample available for theses patients. The purpose of this study is to evaluate the feasibility of molecular profiling for breast cancer metastasis in pleural and peritoneal fluids.

Results

Figure 1
172 Samples of peritoneal and pleural fluids

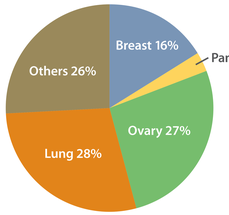

Figure 1: A total of 172 cases were reviewed of which 28 were metastatic breast cancer, 46 were metastatic ovarian cancer, 49 metastatic lung cancer, 5 were metastatic pancreatic cancer and 44 were other type of tumors.

Figure 2
IHC - 28 Breast Cases

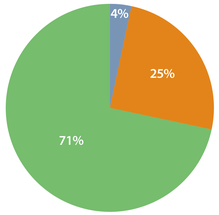

Figure 2: From the 28 breast cases were able to perform at least 10 IHCs in 20 cases, between 1 and 9 IHCs in 1 case and 7 cases were insufficient to performed any IHCs.

Figure 3

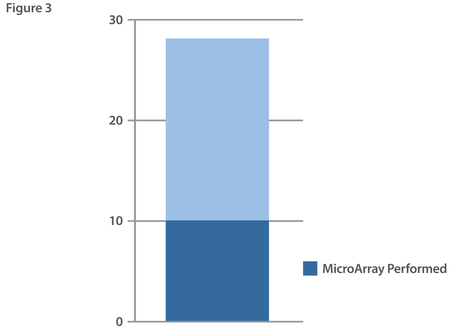

Figure 3: From the 28 breast cases we were able to performed MicroArray RNA gene expression in 10 cases.

Figure 4

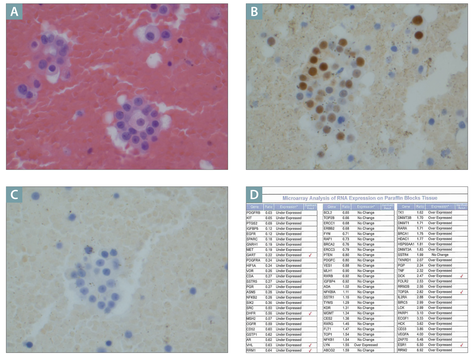

Figure 4: Case of hormone receptor positive Her2 negative breast cancer with MicroArray gene analysis. **A)** H&E; **B)** ER IHC positive; **C)** PR IHC negative; **D)** MicroArray analysis results

Figure 5

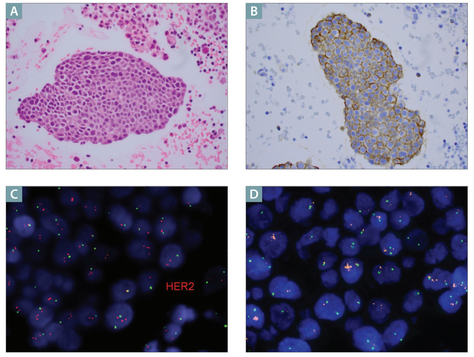

Figure 5: Case of Her 2 positive breast cancer. **A)** H&E; **B)** Her2 IHC positive stained; **C)** Her2 FISH amplified; **D)** Topo2a FISH amplified

Figure 6

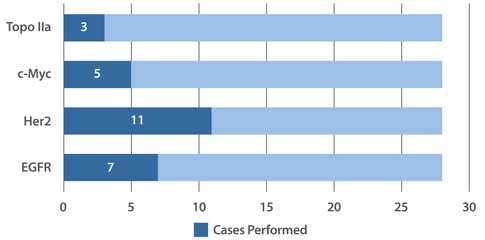

Figure 6: From the 28 breast cases we were able to performed Her2 FISH in 11 cases, EGFR FISH in 7 cases, Topo 2a FISH in 3 cases and c-Myc in 5 cases.

Figure 7

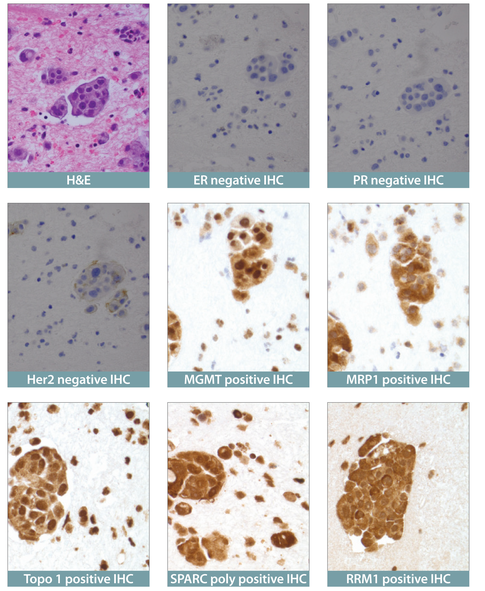

Figure 7: Case of triple negative breast cancer with expression of various biomarkers by IHC.

Figure 8

Agents Associated WITH CLINICAL BENEFIT	Agents Associated With LACK OF CLINICAL BENEFIT
tamoxifen, fulvestrant, toremifene	doxorubicin, liposomal-doxorubicin, epirubicin
anastrozole, letrozole, exemestane, aminoglutethimide	methotrexate
Taxanes	trastuzumab
5-fluorouracil	lapatinib
nab-paclitaxel	erlotinib, gefitinib
cisplatin, carboplatin, oxaliplatin	cetuximab, panitumumab
irinotecan	temozolomide
megestrol acetate, medroxyprogesterone	
sunitinib, sorafenib	
pemetrexed	
gemcitabine	

Figure 8: Example of Caris Target Now report from a hormone receptor positive Her2 negative breast cancer associating biomarker expression with agents with benefit and lack of benefit.

Conclusions

- Molecular profiling of malignant effusions offers additional opportunities for testing when other tissue samples like needle core biopsy or tumor resection are not available.
- Molecular profiling of effusion samples can provide insight into the molecular characteristics of malignant cells.
- Molecular profiling of malignant effusion can provide information to create targeted therapies for cancer.

References

1. Davidson B. Malignant effusions: from diagnosis to biology. *Diagn Cytopathol.* 2004 Oct;31(4):246-54.
2. Von Hoff DD, Stephenson JJ Jr, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol.* 2010 Nov 20;28(33):4877-83.