Highlights From the 13th Annual International Congress on the Future of Breast Cancer®

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Overview

The **International Congress on the Future of Breast Cancer®** was held July 17 – 19 in Huntington Beach, CA. The meeting serves as an update on advances in the breast cancer field with a focus on the clinical implications of the rapid changes in the treatment of breast cancer: novel agents, strategies, and improved regimens. Highlights are provided here of a presentation that was given by Linda D. Bosserman, MD, FACP, about how to re-engineer oncology practices to provide better health for patients, as well as case studies that were shared by faculty chairperson Joyce A. O'Shaughnessy, MD, illustrating patients who were exceptional responders to lapatinib despite primary refractoriness to trastuzumab therapy.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Discuss strategies to improve care for patients with breast cancer
- Review current standards and emerging data regarding systemic therapies for the treatment of early-stage, locally advanced, and metastatic breast cancer.

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The 13th Annual International Congress on the Future of Breast Cancer, held July 17-19, 2014, in Huntington Beach, CA, convened clinicians responsible for the care of patients with breast cancer to help them stay up-to-date regarding the latest breast cancer data, and to learn what will impact practice in the near future. Highlights are provided here of a presentation given by Linda D. Bosserman, MD, FACP, Wilshire Oncology, La Verne, CA, about re-engineering oncology practices to provide better care for patients, as well as case studies that were shared by faculty chairperson Joyce A. O'Shaughnessy, MD, Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, illustrating patients who were exceptional responders to lapatinib despite primary refractoriness to trastuzumab therapy.

Cancer Care and Oncology Practice: Now and in 2015
Re-Engineering for Value

Linda D. Bosserman, MD, FACP

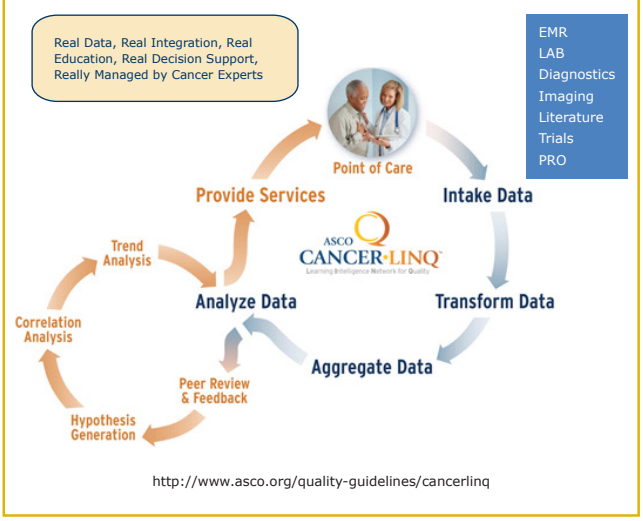
By the year 2028, it will require 100% of an average American family's income to pay their out-of-pocket medical expenses if changes are not made to the healthcare system.[1] To look at healthcare costs in relation to other common items, if the prices of other products had grown as rapidly as healthcare has since World War II, a gallon of milk would cost $48, a dozen eggs would cost $55, and a dozen oranges would cost $138. Spending on cancer specifically has increased from $27 billion to $90 billion since 1990 and continues to rise.[2] Clinicians know best how to allocate resources effectively to improve patient care, so, in Dr. Bosserman's opinion, it is time for clinicians to take back medicine.

One way that clinicians can begin to revamp the healthcare system from within is by using electronic medical records (EMRs) not only to enter data, but, more important, to extract data from the database. In this way, data can be pooled together so that clinicians can continue to gain knowledge. At Dr. Bosserman's institution, after beginning a pilot program using EMR data, they were able to decrease colony-stimulating factor use 14% to 0% in patients for whom this strategy is contraindicated according to the American Society of Clinical Oncology (ASCO), thus saving $505,000. In addition, avoidable hospitalizations were decreased by 19%. Collecting the necessary data, analyzing it, and partnering with health plans can allow an institution to truly examine the issues and lower costs by changing practices that have not been shown to improve outcomes.

Another way to improve patient health is to make healthcare patient-centric, as has been suggested by the Institute of Medicine.[3] As long as the clinician actually addresses symptoms when patients are requested to write them down, then patients are more than happy to do it. The action on the clinician's part is all it takes for the patient to feel engaged; conversely, the patient may feel very disrespected when asked to complete a form that goes unused. This simple practice not only serves to help engage patients in their own care, but also to capture cancer symptoms that may otherwise go unnoticed and untreated, potentially leading to costly interventions or hospitalizations.

ASCO has also prioritized this re-engineering effort by building CancerLinQ™, a cutting-edge health information technology platform that will hopefully revolutionize the treatment of cancer by enabling the cancer community to learn from each of the millions of patients living with cancer nationwide **(Figure)**.[4] This is building a real-time learning environment that can use any EMR, laboratory result, diagnostic, imaging, literature, clinical trial, or patient-reported outcome as input to bring information into the clinic so that clinicians can better prompt patients.

FIGURE. ASCO's CancrLinQ™



Dr. Bosserman encourages all clinician scientists to get involved so that more data can be pooled, and so that its use can be controlled for the best interests of the health of all patients and the advancement of science.

The key to achieving better health lies in data, which are needed to drive decisions. Clinicians should collaborate and agree on the standardized information to be collected—such as diagnosis information, tumor feature, stage, drug regimen, duration of therapy, and features of response and/or relapse—to build the most useful and relevant databases. When all of those data are pooled, continuous improvements can be attained. Costs can be reduced by sharing efficiencies using patient-reported outcomes, health data, and financial data. By making the most of our data,

we can bring available therapies to the appropriate patients, capitalizing on opportunities such as treating exceptional responders such as the ones described next. Behind-the-scenes re-engineering such as this will be needed in order to empower clinicians to improve patient health.

Case Presentations: Exceptional Responders With Metastatic Breast Cancer

Joyce A. O'Shaughnessy, MD

Dr. O'Shaughnessy presented the cases of four patients with inflammatory, trastuzumab-resistant, estrogen receptor (ER)–negative, human epidermal growth factor receptor 2 (HER2)–amplified breast cancer. These patients were treated with preoperative chemotherapy and trastuzumab with no response at all. After showing primary refractoriness to trastuzumab, they were then treated with daily oral lapatinib 1250 mg and achieved slow, partial responses. The patients underwent mastectomy with wide-field radiation therapy while continuing on lapatinib therapy.

All four patients were at high risk for metastatic disease. To date, they have all shown no evidence of disease for 5 or 6 years with no cumulative toxicities, so lapatinib was tolerated well. Three of the four patients have a family history of breast cancer, two of which are known to be negative for *BRCA1* or *BRCA2* mutations, while the fourth patient declined testing. All of the patients qualify as exceptional responders, and informed consent was administered in order to garner tissue and perform genome sequencing. Collaborations with Foundation Medicine and Theranostics Health allowed for a standard 287-gene panel of next-generation sequencing and a phosphoprotein reverse-phase protein microarray assay to characterize HER receptors and downstream pathways.[5] All of the patients had definitive disease (none of them had achieved complete response), and tissue was taken postsurgically. The question is: Can exceptional responder phenotypes identify clinically relevant genotypes?

Patient 1

- A sample was taken after mastectomy. She had already received lapatinib, which was continuing. Sample showed evidence of:
  - *HER2* amplification
  - Phosphatidylinositol-4,5-bisphophate 3-kinase, catalytic subunit alpha (*PIK3CA*) (*H1047R*), *p53*, and *BRCA2* mutations
  - Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and 2B (*CDKN2B*) (*p16*) deletions, which can result in a high proliferative rate
  - *CTNNB1*, *NOTCH 2*, and *NOTCH 3* mutations, as well as amplification of fibroblast growth factor receptor 1 (FGFR1) and CDK6
- Despite these findings, the patient sill had prolonged benefit with lapatinib. High values in the HER family and in the PI3K pathway indicated some pathway activation.

Patient 2

- She received chemotherapy preoperatively and then had a mastectomy pre-trastuzumab. A considerable amount of disease remained after mastectomy, so trastuzumab therapy was begun. While on trastuzumab, she recurred with an inflammatory pattern on her chest wall. Sample showed evidence of:
  - *HER2* amplification
  - *PIK3CA* (*H1047R*), *p53*, and partner and localizer of *BRCA2* (*PALB2*) mutations
  - *CDKN2A* and *CDKN2B* (*p16*) deletions
  - *MCL1* amplification
  - Therefore, this patient had a very similar genotype to patient 1.
  - Prior to trastuzumab, proteome reverse-phase protein microarray assay showed high values for phospho epidermal growth factor receptor (EGFR) and phospho Akt.
  - When she experienced the chest wall recurrence (post-trastuzumab and pre-lapatinib), she showed high values for EGFR, phospho Akt, and phospho S6 kinase, indicating activation of the PI3K pathway.

Patient 3

- A biopsy was performed pre-trastuzumab and pre-lapatinib, along with a mastectomy post-trastuzumab and post-lapatinib. Samples showed evidence of:
  - Initial biopsy HER2 "2+" (80% complete membrane staining), with a HER2/chromosome 17 centromere (CEP17) FISH ratio of 2.4
  - The mastectomy was HER2– by immunohistochemistry (IHC), and there were 5 *HER2* gene copies per cell by FISH.
  - Residual disease was only intralymphatic cancer, so no phospho-protein analysis could be performed.
  - *HER2* was not amplified in either sample via next-generation sequencing.
  - Phosphatase and tensin homolog (*PTEN*) deletion
  - *p53*, *TBX3*, and *BLM* (Bloom's syndrome gene) mutations
  - This patient's activated pathways and phenotype are similar to patients 1 and 2, but with different alterations in the pathways.

Patient 4

- Patient was refractory to preoperative trastuzumab + chemotherapy ± pertuzumab with no response. She did, however,

respond to preoperative lapatinib.
- At mastectomy, she had residual lymphovascular invasion/permeation.
- She remains on lapatinib postoperatively with no evidence of disease.
- She had no family history of breast cancer.
- Sample showed evidence of:
  - HER2 and cyclin D1 amplification
  - Fanconi anemia complementation group A protein (*FANCA*) gene, *PIK3CA E542K*, and *p53* mutations

Pathways to Exceptional Response

There is some convergence around the four pathways found to be activated in these patients: p53, PI3K, homologous recombination (HR), and CDKN2A pathways. Patient 3 showed a mutation in the *BLM* gene, which is in the same HR pathway as *BRCA2* and *PALB2*.[6] In addition, *TBX3*, which was also mutated in this patient, has been found to be a novel driver mutation in breast cancer,[7] along with a negative regulator of p19ARF (the alternate reading frame of the *CDKN2A* gene).[8] So the hypothesis is that *TBX3* is an activating mutation that suppresses ARF/CDKN2A, driving proliferation and/or preventing senescence. Germline sequencing of the *BLM*, which can reveal if it is an allelic loss or a loss in both copies of the gene, showed a polymorphism of unknown significance.

It is possible that in order for a patient to have the exceptional responder phenotype, some type of activation of all four of these pathways is essential. Dr. O'Shaughnessy's hypothesis, which would require further confirmation in the laboratory, is that in patients with these types of aberrations, loss of cell-cycle checkpoints and HR make the loss of EGFR/Akt signaling lethal. Lapatinib may induce further aberration in these patients in the double-strand repair pathway, possibly via *BRCA1*, leaving no ways for DNA to repair itself.[9] This hypothesis is based partially on the finding in triple-negative breast cancer cell lines that lapatinib dissociates *BRCA1* and *EGFR* at sites of DNA damage, and shuttles both *BRCA1* and *EGFR* out of the nucleus and into the cytoplasm.[10]

When DNA is damaged, growth factors try to keep the cell alive, but *PTEN* does not want the cell to divide until the DNA has a chance to repair, so it stops the growth factor signaling. *p16* arrests the cell cycle process, giving the DNA time to repair before the cell enters the G1 phase. Once the cell passes the G1 phase, *p53* gives it a little more time to repair. Then it divides, the DNA replicates, and the cell cycle is completed. It is very important for all of these checkpoints to halt the cell cycle process at different time points to allow the DNA to repair itself.

Lapatinib is an inhibitor of both EGFR (HER1) and HER2, so the hypothesis is that both HER2 and EGFR are both active in the patient cases here with inflammatory breast cancer. Their cells have lost *p16* and *p53*, as well as *BRCA2, PALB2, BLM*, or *FANCA*, leaving another deficit. Therefore, they use *BRCA1* and its partners to repair the DNA protein kinase. In addition, when the p16 and p53 checkpoints are lost, the cell divides rigorously, causing the cell to be under replication stress and accumulate further abnormalities. The cell really needs the growth factor signal. EGFR and HER2 send survival signals through PI3K and Akt. Also, EGFR, Akt1, and the β isoform of PI3K are cytosolic for survival and enhance DNA repair. When the cell is in trouble, the growth factor pathway is essential to help repair the struggling cell.[10,11]

When EGFR and HER2 signaling is knocked out, EGFR and PI3Kβ leave the nucleus and *BRCA1* shuttles to the cytoplasm, where it is pro-apoptotic in a p53-independent manner. Therefore, in theory, the loss of the checkpoints is needed to create a situation of replication stress, as is a defect in HR so that the cells rely on nonhomologous end-joining, and abnormalities in PI3K or PTEN may enhance the growth factor signaling needed in the sick cell, and so all four pathway aberrations may be needed in order to replicate this exceptional lapatinib response phenomenon in inflammatory breast cancer. It may also be worth evaluating whether this genotype could predict lapatinib response or EGFR tyrosine kinase inhibitor (TKI) efficacy in triple-negative breast cancer and other cancers.

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