Breast and gastrointestinal cancer updates from ASCO 2015

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ABSTRACT

This review focuses on the updates presented at the ASCO 2015 symposium in breast and gastrointestinal malignancies. Some were practice changing while others gave us an exciting glimpse into what’s to come in the very near future. Immunotherapy was the buzz word this year with data presented on every tumor site. Data on the efficacy of anti PD-1 agents in colorectal, hepatocellular and gastric cancer were presented. In breast cancer we saw data on a new and exciting therapeutic target in the form of androgen receptor among triple receptor negative breast tumors presented. Positive results of the PALOMA 3 trial were presented that has given women with hormone receptor positive metastatic breast cancer another therapeutic option. Furthermore data on strategies to further improve anti her2 therapy, optimizing of chemotherapy in the early and advanced stage and various strategies to improve endocrine therapy among patients with breast cancer were presented.

Key words: ASCO, breast cancer, colorectal cancer, immunotherapy

INTRODUCTION

Every year, one goes to American Society of Clinical Oncology (ASCO) to hear what is new and happening in oncology. The buzz that literally sweeps through the thousands of health care professionals that are involved in the care of patients with cancer who attend this prestigious symposium is something we all wait for. This review focuses on the updates presented in breast and gastrointestinal (GI) malignancies. Truly exciting results were presented. Some were practice changing while others gave us an exciting glimpse into what is to come in the very near future. Immunotherapy was the buzzword this year with data presented on every tumor site. Data on the efficacy of anti PD-1 agents in colorectal, hepatocellular, and gastric cancer were presented. In breast cancer, we saw data on a new and exciting therapeutic target in the form of androgen receptor among triple receptor negative breast tumors presented. Positive results of the PALOMA 3 trial were presented that has given women with hormone receptor positive metastatic breast cancer another therapeutic option. Furthermore data on strategies to further improve anti her2 therapy, optimizing of chemotherapy in the early and advanced stage and various strategies to improve endocrine therapy among patients with breast cancer were presented.

BREAST CANCER UPDATES

Optimizing chemotherapy strategies

Over the last decade, we have seen significant strides in the management of women with metastatic breast cancer converting an essentially incurable disease into a chronic one. Several chemotherapeutic agents have been introduced, each providing an option for women with metastatic breast cancer. Based on improvement in overall survival, Eribulin has recently received Food and Drug Administration (FDA) approval for the treatment of women with heavily pretreated metastatic breast cancer. This year at ASCO, Perez et al. presented the results of the phase III BEACON trial[1] that randomized women with advanced breast cancer whose disease had progressed on anthracyclines, taxanes, and capecitabine to either physician choice of chemotherapy or the etirinotecan pegol (EP) — a long-acting topoisomerase I inhibitor. The authors reported a 2.1-month improvement in overall survival favoring the cohort that received EP, however, this was not statistically significant ($P = 0.08$). Interestingly, in a prespecified subgroup analysis, the investigators observed a doubling in the overall survival from 4.8 months to 10 months ($P = 0.009$) among women with a history, treated brain metastases indicating potential central nervous system activity of EP.

Chemotherapy is the standard of care among women with triple-negative breast cancer in both the early stage and the advanced setting. Ixabepilone has been extensively investigated among women with metastatic breast cancer with meta-analysis indicating that it may be particularly useful among women with triple-negative breast cancer. Yardley et al.[3] presented the results of the phase III TITAN trial that randomized women with early stage triple-negative breast cancer who had received...
adriamycin and cyclophosphamide (AC) to either ixabepilone or paclitaxel in the adjuvant setting. The authors reported disease free survival of 88% among those who received AC/ixabepilone and 89% among those who received AC/paclitaxel thereby, demonstrating no advantage of ixabepilone over paclitaxel in the adjuvant setting in this cohort.

**Improving endocrine therapy strategies**

Tamoxifen has often been used among women with hormone receptor-positive ductal carcinoma in situ (DCIS), following locoregional management where it has been shown to reduce recurrence rates with no impact on overall survival. Margolese et al.[3] presented the results of the NSABP-35 phase III trial that randomized postmenopausal women with hormone receptor-positive DCIS who had undergone lumpectomy and radiation therapy to either tamoxifen or anastrozole. The authors reported a significant improvement in 10-year breast cancer-free interval favoring the group receiving anastrozole (hazard ratio [HR] = 0.73, 93.5% vs. 89.2%, P = 0.03).

Two important abstracts were presented at ASCO 2015 looking at methods of improving the efficacy of endocrine therapy among women with hormone receptor-positive metastatic breast cancer. Dickler et al.[4] presented the results of the phase III CALGB 40503 trial that looked at the addition of bevacizumab to letrozole as first-line endocrine therapy. In this multicenter trial that enrolled over 300 women with hormone receptor-positive metastatic breast cancer, the authors reported that the addition of bevacizumab to letrozole improved progression-free survival (HR = 0.74, 95% confidence interval [CI]: 0.58-0.95, P = 0.016) compared to letrozole alone. Furthermore, no significant difference was observed with regards to overall survival between the two groups. Palbociclib, a cyclin-dependent kinase 4/6 inhibitor, has recently received FDA approval in combination with letrozole as first-line therapy for hormone receptor-positive metastatic breast cancer. Turner et al.[5] presented, as a late-breaking abstract, the results of the phase III PALOMA-3 trial that looked at the addition of palbociclib to fulvestrant among pre- and post-menopausal women with hormone receptor-positive metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer that had progressed on prior endocrine therapy. Premenopausal women received goserelin. Median progression-free survival was significantly improved with the addition of palbociclib from 3.8 months to 9.2 months (HR = 0.42, 95% CI: 0.32-0.56, P < 0.001). Most common side effects reported with the addition of palbociclib included neutropenia, leukopenia, anemia, thrombocytopenia, and fatigue. These two abstracts raised several important questions that have clinical implications. Does bevacizumab have a role among women with metastatic hormone receptor-positive breast cancer? In an endocrine resistant population, should everolimus or palbociclib be the agent of choice? What toxicities will be observed among patients taking everolimus following progression on palbociclib?

**Improving anti-human epidermal growth factor receptor 2 therapy strategies**

The landscape of HER2-positive breast cancer has certainly changed over the last two decades. The introduction of anti-HER2 therapy has significantly improved the prognostic outcome of this cohort in both the early stage and the advanced setting. As such research efforts have focused on trying to improve further prognostic outcome with the development of novel anti-HER2 agents and looking at novel combinations of these agents.

Ellis et al.[6] presented the results of the phase III MARIANNE trial that randomized women with HER2 positive metastatic breast cancer to trastuzumab and taxane, TDM-1 plus placebo or TDM-1 plus pertuzumab. Median progression-free survival among the three groups was reported to be 13.7 months, 14.1 months, and 15.2 months, respectively. Although noninferiority of the TDM-1 containing arms compared to trastuzumab and taxane was demonstrated, superiority was not observed. The CLEOPATRA trial has clearly shown that the addition of pertuzumab to trastuzumab and taxane improves prognostic outcome. The addition of pertuzumab to TDM-1 did not improve prognostic outcome over trastuzumab and taxane as demonstrated by MARIANNE, suggesting that we need to be cautious when combining targets that may not only be associated with an increase in adverse events but also would be associated with a significant financial toxicity with no associated survival benefit.

Adjuvant trials have shown that the addition of 1 year of trastuzumab significantly improves prognostic outcome among women with early stage HER2-positive breast cancer. The HERA trial is not reported significant benefit when giving 2 years of adjuvant trastuzumab compared to 1 year. Chan et al.[7] reported on the results of the phase III placebo-controlled ExteNET trial that randomized patients with stage I-III HER2-positive breast cancer who had completed adjuvant chemotherapy and trastuzumab to receive either 1 year of neratinib (a pan HER tyrosine kinase inhibitor) or 1 year of placebo. At the primary analysis conducted at 2 years, the authors reported a significant improvement in invasive disease-free survival favoring the group receiving neratinib (93.9% vs. 91.6%, HR = 0.67, 95% CI: 0.50-0.91, P = 0.0046). Further follow-up is required before we can determine the impact on clinical practice.

**Refining triple-negative breast cancer at the molecular level**

Triple-negative breast cancer is considered the most aggressive subtype of breast cancer. We know that it not
only associated with a worse prognostic outcome but associated with early recurrence; in the clinic, it has no specific targets and, thus, chemotherapy is a standard of care and is in itself a heterogeneous disease composed of a number of subtypes, each with its own unique prognostic outcome. This year at ASCO, important questions were addressed with regards to this subtype of breast cancer. Pathological complete response is an important surrogate marker for prognostic outcome, especially among patients with triple-negative breast cancer. Patients with triple-negative breast cancer who have residual disease postpreoperative chemotherapy are known to have worse outcome. Can we identify a cohort of women with low risk of recurrence who has residual disease postpreoperative chemotherapy? Miyashita et al. looked at the prognostic significance of number biomarkers in the residual tumors of 131 patients with triple-negative breast cancer who had received preoperative chemotherapy. The authors demonstrated that the presence of high CD8+ tumor infiltrating lymphocytes levels or the presence of high CD8+/FOXP3+ ratio was associated with a significantly improved recurrence-free and breast cancer-specific survival. Interestingly, the investigators further demonstrated that an increase in CD8+/FOXP3+ ratio after preoperative chemotherapy was also associated with improved prognostic outcome. These parameters may be used to classify residual triple-negative tumors postpreoperative chemotherapy into two prognostic categories (i.e., high versus low risk of early recurrence). The next question would be, whether those at high risk of recurrence are candidates for further systemic therapy. Can we use the heterogeneous biology of triple-negative breast cancer to identify a specific target for therapeutic intervention in this cohort? Traina et al. presented the results of an interesting phase II trial that looked at targeting androgen receptor among patients with metastatic triple receptor-negative breast cancer. The initial results of this study were first presented at the San Antonio Breast Cancer Symposium 2014 where the authors demonstrated that 79% of the triple-negative breast tumor samples had some level of androgen receptor expression with 55% demonstrating >10% expression of androgen receptor expression. At ASCO 2015, the investigators presented results looking at efficacy of enzalutamide among triple receptor-negative tumors that expressed androgen receptors. Among 75 evaluable patients, 35% had clinical benefit at week 16 and 29% had clinical benefit at week 24. The investigators further developed an androgen receptor gene signature that could identify patients most likely to benefit from enzalutamide. **GASTROINTESTINAL CANCER UPDATES** Is immunotherapy the new kid on the block? Immunotherapy was a hot topic at ASCO 2015 with data presented in almost every tumor site. The most exciting results were within the realm of GI malignancies where three important abstracts were presented. Le et al. presented the results of the phase II study KEYNOTE-164 trials that looked at blocking PD-1 with pembrolizumab among 41 patients with progressive metastatic cancer. Three cohorts of patients were enrolled: Patients with colorectal cancer whose tumors were mismatch repair (MMR) proficient, patients with colorectal cancer whose tumors were MMR-deficient, and patients with other cancers whose tumors were MMR-deficient. Pembrolizumab was given at a dose of 10 mg/kg every 2 weeks. Immune-related objective response rate was 40% and 0% among patients with colorectal tumors whose tumor was MMR-deficient and proficient, respectively. A 20-week immune-related progression-free survival was 78% and 11% among patients with colorectal tumors whose tumors were MMR-deficient and proficient, respectively. Patients with MMR-deficient noncolorectal tumors had results similar to those with colorectal MMR-deficient tumors. Furthermore, the investigators also demonstrated that MMR-deficient tumors had a significantly higher burden of somatic mutations compared to MMR-proficient tumors ($P=0.007$) with high somatic mutation loads being associated with higher progression-free survival ($P=0.02$).

In a late breaking abstract presentation, El-Khoueiry et al. presented the phase I/II CheckMate-40 study that looked at the efficacy of the anti-pd-1 inhibitor nivolumab among patients with advanced hepatocellular carcinoma whose Child–Pugh score was <7 and who had progressed on prior systemic therapy. Patients with hepatitis B were allowed to enroll in the study, so long as they were on anti-viral therapy. The authors reported that among 42 evaluable patients, overall response rate was 19%, and stable disease was observed in 48% of the patients. Among 20 evaluable patients with stable, disease range of duration of response was 1.1-17.3 months. Preliminary 12 months overall survival was estimated at 62%. These results are encouraging with nivolumab currently being investigated in this setting in an expansion cohort phase of this study. Bang et al. presented the results of the KEYNOTE-012 multicenter open label phase I b trial that looked at the efficacy of pembrolizumab among 39 patients with PD-L1-positive metastatic or recurrent adenocarcinoma of the stomach or gastroesophageal junction. The investigators reported an overall response rate of 33%, a median time to response of 8 weeks and median response duration of 40 weeks. Median progression-free survival and overall survival were 1.9 months and 11.4 months, respectively.
Colorectal cancer updates

Several important abstracts were presented regarding the management of patients with colorectal cancer. Yanhong et al. presented the results of the multicenter FOWARC trial that randomized nearly 500 patients with locally advanced rectal cancer to receive 5-Fluorouracil and radiation therapy, mFOLFOX-6 and radiation therapy, or mFOLFOX-6 alone. The authors reported a pathological complete response rate of 12.5%, 31.3%, and 7.4%, respectively (P = 0.001). The addition of radiation therapy to chemotherapy was associated higher rates of toxicity and postoperative complications.

Gibbs et al. presented the results of the phase III SIRFLOX trial that randomized 530 patients with metastatic colorectal cancer and liver metastases to received first line mFOLFOX6 with or without bevacizumab and with or without selective internal radiation therapy (SIRT). Progression-free survival was similar between the groups. Liver-specific progression, however, was improved among patients who underwent SIRT compared to those who did not (20.5 vs. 12.6 months, P = 0.02). This trial provides evidence for the use of radioembolization in an earlier line setting among patients with metastatic colorectal cancer.

Approximately, 5% of the patients with metastatic colorectal cancer have HER2-positive disease. The role of anti HER2 therapy among patients with HER2-positive metastatic colorectal cancer has recently been the focus of research. Siena et al. presented the results of phase II HERACLES trial that looked at the efficacy of trastuzumab and lapatinib among 25 patients HER2 amplified metastatic colorectal cancer that were resistant to standard therapeutic regimens. The authors reported 8 patients to have an objective response and median time to progression was 5.5 months.

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Conflicts of interest
There are no conflicts of interest.

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