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Updates from the 2014 San antonio breast cancer symposium

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ABSTRACT

The san antonio breast cancer syposium (SABCS 2014) was an exciting one this year. Data from the SOFT trial was presented that had potential implications on the treatment of pre menapausal women with hormone receptor positive breast cancer. In a phase II trial fulvestrant was found to significantly improve progression free and overall survival compared to anastrazole in the first line treatment of women with hormone receptor positive metastatic breast cancer. We saw a number of intersting abstracts looking at trying to refine the role of platinums and exploring the role of blocking PD-1 among women with triple receptor negative breast cancer. We also saw the results of a number of trials trying to refine standard chemotherapeutic regimens. Here we will review some fon the most interesting abstracts presented this year at SABCS 2014.

Key words: *Breast cancer, ovarian suppression, triple negative, targeted therapy*

INTRODUCTION

2014 has certainly been an exciting year in the realm of breast cancer management. At ASCO 2014 we saw the results of the combined analysis of the SOFT/TEXT trials that was presented at the plenary session. The combined analysis asked the fundamental question of whether an aromatase inhibitor was superior to tamoxifen among premenopausal women with hormone receptor positive early stage breast cancer. At the SABCS 2014 symposium, we got to see very important results of the SOFT trial, which asked the question of whether ovarian function suppression added benefit when combined with tamoxifen among premenopausal women. Research efforts to refine the role of paltinums and to find novel therapeutic targets were also presented at SABCS 2014. We also saw results of trials trying to refine standard chemotherapeutic regimens. Here we review some of the interesting abstracts presented at the SABCS 2014.

PROGRESS IN THE MANAGEMENT OF HORMONE RECEPTOR POSITIVE BREAST CANCER

Over the last decade, we have seen a number of important advances made in the management of women with hormone receptor positive breast cancer both in the adjuvant and metastatic setting. In the metastatic setting, we have seen the positive impact on prognostic outcome with the introduction of agents that can over come endocrine resistance in the form of mammalian target of rapamycin (mTOR) inhibitors such as everolimus. The addition of the cyclin-dependent kinase 4/6 inhibitor palbocilib to letrazole as a first line treatment of women with estrogen receptor positive metastatic breast cancer has resulted in unprecedented significant improvement in progression free survival compared to single agent letrazole in a phase II randomized clinical trial.[1] This year at the SABCS we saw a number of presentations that attempted to answer two important questions in the metastatic setting. The first question attempts to address the vital issue of what is the optimal endocrine agent to use in the first line setting? Robertson *et al.*[2] presented the results of the "FIRST" phase II study that randomized patients with estrogen receptor positive metastatic breast cancer to either 500 mg of fulvestrant or anastrazole in the first line setting. The primary end point of this study was clinical benefit rate, which was not significantly different between the two arms of the study (72.5% [fulvestrant] vs. 67.0% [anastrazole], $P = 0.386$). The authors further demonstrated significant improvements in progression free survival (23.4 months vs. 13.1 months, $P = 0.01$) and overall survival (54.1 months vs. 48.4 months, $P = 0.041$) favoring the group of patients receiving fulvestrant. Although the results of the FIRST trial are provocative the definitive answer as to which endocrine agent is the optimal first line treatment will come from the ongoing placebo controlled phase III FALCON trial that is randomizing patients with estrogen

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receptor positive metastatic breast cancer to either 500 mg of fulvestrant or anastrzole.

The second important question in the metastatic setting addressed was could we improve on the efficacy of existing endocrine agents? Krop *et al.*[3] presented the results of the phase II FERGI study that randomized patients with metastatic breast cancer who had received a prior aromatase inhibitor either in the adjuvant or metastatic setting to either 500 mg of fulvestrant combined with the PI3Kinase inhibitor pictilisib or fulvestrant and placebo. In the intent to treat population, the authors reported that the addition of pictilisib to fulvestrant was associated with a nonsignificant improvement in progression free survival (5.1 months vs. 6.6 months, $P = 0.09$). Furthermore, the authors reported that the presence of PI3K mutation did not predict benefit from the addition of pictilisib. In an unplanned exploratory analysis the authors observed potential activity with improvement in progression free survival with the addition of pictilisib among patients who had ER and PR positive disease (3.7 months vs. 7.4 months). Adelson *et al.*[4] reported on a phase II trial that randomized women with metastatic breast cancer who had received aromatase inhibitors either in the adjuvant or metastatic setting to either fulvestrant and bortezomib or fulvestrant alone. The authors reported that the addition of bortezomib did not improve the median or 6 months progression free survival, but significantly improved the 12 months progression free survival rate from 14% to 28% ($P = 0.03$). These hypothesis generating results indicate that targeting the proteasome may help increase the time needed to develop an acquired resistance to endocrine agents.

Over the last 2 years, we have seen the results of several important large randomized clinical trials addressing the important question of optimal endocrine management of women with estrogen receptor positive early stage breast cancer. In 2013 we saw the results of the ATLAS and ATTOM trials that showed that 10 years of endocrine therapy was superior to 5 years. At ASCO 2014 we saw the results of the combined analysis of the SOFT and TEXT trials where premenopausal women with estrogen receptor positive early stage breast cancer were randomized to receive either tamoxifen and ovarian function suppression or exemestane and ovarian function suppression. The combined analysis results revealed an absolute improvement in disease free survival of 3.8% at 5 years favoring the group receiving exemestane and ovarian function suppression. This year at SABCS we saw the results of the SOFT trial that randomized premenopausal women to either tamoxifen alone, tamoxifen and ovarian function suppression or exemestane and ovarian function suppression.[5,6] Approximately, 1000 women were enrolled in each arm of the study. The primary analysis was to look at disease free survival among women who received tamoxifen and tamoxifen plus ovarian function suppression. The authors reported that overall at a median follow-up of 5.6 years the addition of ovarian function suppression to tamoxifen did not benefit premenopausal women compared to tamoxifen alone ($P = 0.10$) indicating that some women do well with tamoxifen alone. In a preplanned analysis the authors further observed that among premenopausal women who had sufficiently high risk of recurrence to receive adjuvant chemotherapy the absolute improvement in 5 years breast cancer free interval was 4.5% among women who received tamoxifen and ovarian suppression and 7.7% among women who received exemestane and ovarian suppression when compared to tamoxifen alone respectively. Among premenopausal women who did not receive adjuvant chemotherapy (who had low risk clinicopathological features of disease) the absolute improvement in 5 years breast cancer free interval was >95% across all three arms of the study. In an unplanned analysis of 350 women under the age of 35 years, 94% of whom received chemotherapy, the authors reported a 5 years breast cancer free interval of 67.7%, 78.9%, 83.4% among women who received tamoxifen, tamoxifen plus ovarian function suppression and exmestane plus ovarian function suppression respectively. The authors concluded that premenopausal women at sufficiently high risk of recurrence to warrant chemotherapy and who retain premenopausal estradiol levels the addition of ovarian function suppression to tamoxifen reduced risk of recurrence. The use of ovarian function suppression enabled the use of an aromatase inhibitor, which could provide further risk reduction in higher risk cohorts. The addition of ovarian function suppression however was associated with more side-effects in the form of menopausal symptoms, depression, osteoporosis, hypertension, and diabetes. The results of these large adjuvant endocrine therapy trials have no doubt been practice changing. However, several questions remain some of which include how long should endocrine therapy be given when ovarian function suppression is used and how long should ovarian function suppression be given if one were to consider going beyond 5 years of endocrine therapy in a woman who continues to be premenopausal. Regardless at present time it is vital to tailor treatment according risk factors such as age and clincopathological factors. It is also vital that the patient be made of the decision making process and that she understands the associated side effect profile.

BREAKING NEW GROUND IN TRIPLE NEGATIVE BREAST CANCER

The most significant advance made in the last decade in the realm of breast cancer has been the understanding that

this is a heterogenous disease composed of a number of subtypes each associated with a unique natural history and prognostic outcome. Major advances have been made with regards to endocrine therapy for patients with hormone receptor positive breast cancer and the introduction of several anti HER2 agents has changed the natural history of HER2 positive breast cancer. Unfortunately, no targeted therapy are available for women triple negative breast cancer and the prognostic outcome associated with this subtype compared with other subtypes continues to be poor. As such a number chemotherapeutic agents have been investigated in the realm of triple negative breast cancer. Last year at the ASCO 2013 and SABCS 2013 we saw the results of the gepartsixto and CALBG 40603 phase II trials that showed that the addition of carboplatin to neoadjuvant chemotherapy increased pathological complete response rates among patients with triple negative breast cancer. The question then arose as to whether biomarkers were present to predict for platinum benefit in this group. Recent data from the geparsixto revealed higher pathological response rates among patients with lymphocyte predominant triple negative breast cancer and among patients whose tumors expressed immunologically relevant genes. This year at SABCS further analysis using tissue derived from the CALGB 40603 phase II trial (a 2 × 2 factorial trial that randomized patients with triple negative breast cancer who all received paclitaxel to receive in addition either carboplatin or bevacizumab) were presented.[7] The investigators looked at the impact of intrinsic subtype and other gene signatures and its association with pathological complete response rate. The authors reported no interaction between intrinsic subtype or expression immune signatures reflecting tumor infiltrating lymphocytes and increase in pathological complete response rate with the addition of carboplatin.

The role of platinum in metastatic triple negative breast cancer was also investigated. The results of the phase III TNT trial that randomized patients with triple negative or BRCA 1/2 mutation positive metastatic breast cancer to either first line treatment with docetaxel or single agent carboplatin were presented.[8] Primary end point was objective response, and secondary end points included progression free survival and overall survival. Median follow-up was 11 months. The authors reported that in the overall cohort there was no significant difference in the objective response, progression free survival and overall survival. Among patients with mutations in BRCA 1 or 2 the authors observed an increase in objective response (68.0% vs. 33.3%, P = 0.03) and in progression free survival (6.8 months vs. 4.8 months) favoring the group of patients receiving carboplatin.

With two phase II trials looking at incorporating platinums in the neoadjuvant setting and one phase III looking at its role in the first line treatment in the metastatic setting among patients with triple negative breast cancer the question arises as to whether platinums should be standard of care among women with this subtype of breast cancer. Indeed the results are provocative and hypothesis generating. However, it is clear that not all patients with triple negative breast benefit from platinumsand that the addition of this addition to standard regimens is associated with increased toxicity. The key will be to identify subgroups who will be particularly sensitive to this agent. The presence of BRCA mutation maybe one subgroup to investigate further.

Blocking of PD-1 is also being actively investigated in the treatment of triple negative breast cancer. Results of the phase Ib KEYNOTE trial that investigated the use of pembrolizumab, a humanized IgG4 high affinity anti-PD1 antibody was presented.[9] This trial enrolled patients with triple receptor negative recurrent or metastatic disease whose tumor expressed PD-L1. In this heavily pretreated group the authors reported an overall response rate of 18% and a 6 months progression free survival of 23.3%. Responses were reported to be durable with a median duration of response not reached with three out of the five responders on treatment for more than 11 months.

REFINING TREATMENT OF HER2 POSITIVE BREAST CANCER

The introduction of trastuzumab, a monoclonal antibody targeting HER2, has changed the natural history of HER2 positive breast cancer impacting prognostic outcome positively in the both the adjuvant and metastatic setting. Several new anti HER2 agents have been introduced including trastuzumab emtansine (TDM-1), pertuzumab and lapatinib. Efforts are underway to find ways to further improve prognostic outcome in this subgroup by optimally using these anti HER2 agents and finding methods to overcome resistance that eventually develops to these anti-HER2 agents. One method of overcoming resistance is to add an mTOR inhibitor. This concept was investigated in the BOLERO-1 trial, a phase III trial that randomized women with HER2 positive metastatic breast cancer who had not received prior chemotherapy to either trastuzumab and paclitaxel or the same combination with everolimus.[10] The primary end point was progression free survival. The authors reported that in the overall cohort there was no difference in progression free survival between the two arms of the study. However in the subgroup with HER2 positive, hormone receptor

negative breast cancer the addition of everolimus resulted a 7 months improvement in progression free survival (20 mos with everolimusvs 13 mos with placebo; HR: 0.66; P =.0049) but this did not reach statistical significance threshold based on trial design (P = 0.044). The addition of everolimus was associated with a higher rate of adverse event related on treatment related deaths (3.6% for everolimus vs. 0% for placebo).

Another question that has been the focus of research is whether chemotherapy can be omitted among patients with early stage HER2 positive breast cancer. One subgroup that this may be feasible are patients hormone receptor positive/HER2 positive breast cancer. This concept was the basis of the TBCRC023 phase II trial that enrolled patients with stage II and III HER2 positive breast cancer who were randomized to receive either 12 weeks or 24 weeks of neoadjuvant trastuzumab and lapatinib.[11] Patients with estrogen receptor positive disease in addition received neoadjuvant endocrine therapy. The authors a two-fold numeric increase in pathological complete response rate in the 24 weeks cohort compared to the 12 weeks cohort. This difference was more than three fold in the ER positive cohort (9% vs. 33%).

IMPROVING EXISTING CHEMOTHERAPY REGIMENS

Results of several trials looking at methods of improving adjuvant and neoadjuvant chemotherapeutic regimens were presented this year. The geparsepto trial is a phase III trial that randomized women with early stage breast cancer to receive neoadjuvant paclitaxel followed by epirubicin, cyclophosphamide (EC) or abraxane, followed by EC.[12] Patients with HER 2 positive breast cancer in addition received neoadjuvant trastuzumab and pertuzumab throughout the course of neoadjuvant chemotherapy. The authors reported an overall increase in pathological complete response rate from 29% to 38% favoring the cohort receiving abraxane (P = 0.001). Although an increase in pathological complete response was seen across all subtypes of breast cancer, this was particularly striking among patients with triple negative breast cancer (25.7% vs. 48.2%, P < 0.001). The authors further reported an increased incidence of neuropathy with abraxane compared to paclitaxel. Long term follow-up will be needed to determine if the increase in pathological complete response will translate in an improvement in prognostic outcome.

A question that has been repeatedly asked is what is the optimal duration chemotherapy and type of anthracycline among patients with node negative early stage breast cancer. The NSABP-36 is a phase III trial that randomized women with node negative early stage breast cancer to either four cycles of adjuvant adriamycin, cyclophosphamide (AC) or 6 cycles of adjuvant 5-FU, epirubicin, cyclophosphamide (FEC) 100.[13] Following completion of chemotherapy patients with HER2 positive disease received trastuzumab and those with hormone receptor positive disease received endocrine therapy. The primary end point of this trial was disease free survival. The authors reported no difference in either disease free or overall survival. The use of 6 cycles of FEC 100 with increased toxicity compared to four cycles of AC.

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Annual ISMPO Meeting 2014, 26th -28th December, Kolkata: Orations and Awards

1 – Dr. Purvish M Parikh, Mumbai. Title of oration: Oncology in 2020 – Personalized, Precision or Pragmatic.

2 – Dr. Dinesh Chandra Doval, Delhi. Title of oration: Oncology Clinical Research in India- Past, present & future.

3 – Principal Amritlal Pairkh Award (cheque for Rs 25,000) – Dr. Kumar Prabhash, Mumbai.

4 – Dr. Kella Venkata Award for best oral paper presentation (cheque for Rs 30,000) – Dr. Mangesh P Kamath, Bengaluru (Kidwai). Abstract titled Metastatic Lung Cancer In A Regional Cancer Center Study: Demographic analysis and Pharmacoeconomics

5 – CK Handoo Award for second best oral paper presentation (cheque for Rs 20,000) – Dr. Dhanraj KM, Pondicherry (JIPMER). Abstract titled comparison of efficacy and toxicity profile of neoadjuvant chemotherapy FEC 100 and Docetaxel 75 versus AC and Docetaxel in Locally Advanced Breast Cancer

6 – CK Handoo Award for best poster presentation (cheque for Rs 15,000) – Dr. Ranjith Kumar, Pondicherry (JIPMER). Abstract titled Prospective audit of morbidity in patients receiving chemotherapy in department of Medical Oncology of a tertiary care cancer center

7 – Debate Competition: Winners A) Dr. Vishwanath Sathyanarayanan, Bengaluru 2) Dr. Mangesh P Kamath, Bengaluru