Perspectives on Geriatric Oncology Research Presented at the 2020 San Antonio Breast Cancer Symposium

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1. Introduction

The 2020 San Antonio Breast Cancer Symposium (SABCS) united healthcare professionals and researchers from all over the globe to showcase the cutting-edge in breast cancer research. Despite the COVID pandemic, many advancements and significant clinical findings on breast cancer were announced in this year's virtual symposium. Here, we feature research relevant to geriatric oncology.

2. Geriatric Oncology Specific Research

The 10-year results of the Prime 2 randomized trial evaluating whole breast irradiation (WBRT) in women 65 years or older with early breast cancer showed no difference in overall survival (OS) and no difference in metastasis free survival between those patients who received adjuvant WBRT and those who did not.[1] The patients included in this study had an average age of 71. All patients had hormonal receptor (HR)-positive disease, tumor size $\leq$3 cm (88% T1 disease), pathologically node negative, the vast majority (95%) were grade 1-2, and all received breast conserving therapy and neoadjuvant and/or adjuvant hormonal therapy. The risk of local recurrence was higher in the no WBRT group (9.8% vs. 0.9% p=0.00008) but OS was unchanged (80.4% vs. 81%). This proves reassuring that omitting WBRT for older adults with early invasive breast cancer is a reasonable approach as it does not compromise survival. Interestingly, a subset analysis of the no WBRT group revealed that the risk of local recurrence increased to 19% in patients with low estrogen receptor (ER) positivity compared to 9.2% in those with high ER positivity, suggesting that the patients who benefit most from omitting WBRT are those considered to be low risk with clearly luminal features.

A Canadian group led by Dr. McKevitt presented data during a poster discussion proposing sentinel lymph node biopsy (SLNBx) should not be routine in patients 70 years or older with ER+ human epidermal growth factor receptor 2 (HER2)-negative disease, consistent with the Choosing Wisely Campaign recommending no SLNBx in this patient population. They found that of 2,662 patients undergoing upfront surgery with SLNBx, 23% had a positive SLNBx, and this was associated with older age, higher grade, larger tumor, and positive LVI. The 5-year breast cancer specific survival (BCSS) was excellent at 96%, and this was similar between the SLNBx positive and SLNBx negative groups. However, this only held true when patients received adjuvant hormone therapy (HT), as patients with a positive SLNBx who did not receive HT had a lower BCSS (Hazard ratio (HR) 3.22, 95% CI 1.24-8.42) compared to those with a negative SLNBx. Furthermore, a very low-risk group was identified as those aged 75-79 with a grade 1-2 tumor <2 cm with a 5-year BCSS $\geq$95% with or without positive SLN and with or without HT. These data

support omitting SLNBx in this population where SLN status is not necessarily needed to determine adjuvant therapy, particularly in the very low-risk group even in the absence of planned HT. This may become an increasingly important consideration as the fit older population continues to benefit from surgery as per guidelines, as highlighted by poster PS1-07.

3. Practice Changing Researches Relevant to Older Patients

3.1 Early breast cancer

(a) low risk HR+/HER2- early breast cancer: Can we omit chemotherapy?

The SWOG S1007/RxPONDER study randomised 5,015 patients with stage II-III ER+ HER2-negative breast cancer, 1-3 involved lymph nodes and a Recurrence Score (RS) 0-25 to receive chemotherapy followed by endocrine therapy versus endocrine therapy alone.[2] At a median follow-up of 5.1 years, no benefit was seen for chemotherapy in postmenopausal women (5-year invasive disease-free survival (IDFS) rate 91.9% on chemotherapy vs. 91.6% on endocrine therapy alone; HR 0.97, p 0.82). No differential effect of chemotherapy was seen across age groups in the postmenopausal cohort (≥65 years: HR 1.00; 55-64 years: HR 0.87; ≤55 years: 1.24). The study suggests that node positivity, while an important prognostic marker, is not a predictive marker of chemotherapy sensitivity. These results are key to inform treatment decisions in older patients who typically have a higher risk of toxicities.

To this purpose, the results presented by Sparano et on a study validating the use of RSClin^{TM} model are useful for the older age group. The model integrates the 21-gene expression assay and clinical-pathological features and was able not only to provide more prognostic information compared to its two individual components, but also to improve their performance in predicting chemotherapy benefits in HR+ HER2- node-negative breast cancer patients.

An updated analysis of the MINDACT study was also presented. In this study, patients with clinical low risk and genomic low risk had an excellent distant metastasis-free survival (DMFS) rate at 8 years (94.7%) without chemotherapy, whereas those with clinical low and genomic high risk had a 3.6% decrease in DMFS compared with the low/low cohort. Although this analysis was clearly underpowered, a 1.5% benefit with chemotherapy was seen in this specific cohort. The magnitude of these effects is crucial to consider when discussing options especially with older patients, where survival benefit may be smaller.

(b) High risk HR+/HER2- breast cancer: role of adjuvant CDK4/6 inhibitors

The monarchE study showed a positive signal for adjuvant abemaciclib in patients with high-risk (> 4 nodes or 1-3 nodes and either grade 3 disease or tumor size at least 5cm, or centrally

assessed Ki-67 levels >20%) early breast cancer.[3] At median follow-up of 19 months, the 2-year IDFS rates were 92.3% for 2808 patients in the abemaciclib and endocrine therapy arm and 89.3% for 2829 patients in the endocrine alone arm (an absolute difference of 3%, HR 0.71, 95% 0.58-0.87, p=0.0009). In contrast, the PENELOPE-B trial, did not show a positive outcome with adjuvant palbociclib for 1 year plus endocrine therapy in patients who had a less than pathologic complete response following neoadjuvant taxane-containing chemotherapy.[4] At a median follow-up of 43 months, there was no difference in IDFS seen between 628 patients treated with palbociclib in combination with endocrine therapy and 616 patients treated with endocrine therapy alone (73% vs 72.4%, an absolute difference of 0.6%, HR 0.93, 95% CI 0.74-1.17, p=0.525). Although monarchE shows a positive signal with abemaciclib in high-risk early breast cancer, it is early data and one has to be cautious, particularly given that PENELOPE-B study did seem to have an early signal of benefit (an absolute difference of 4.3% for IDFS) at 2 years which was diminished with longer follow-up (dwindled to 0.6% by 4 years). It remains unclear if the observed benefit of abemaciclib in monarchE will continue with longer follow-up, resulting in a different outcome than PENELOPE-B and perhaps suggesting that abemaciclib is a different agent, with more potency to CDK4/6 inhibition, or perhaps the longer duration exposure effect will have a better benefit. Additionally, we await further data from ongoing trials (NCT03633331, NCT04305834) to understand the safety and tolerability of palbociclib and abemaciclib in the severely underrepresented population of older adults in clinical trials, measuring both the incidence of grade 3-5 toxicities as well as the effects of these toxicities on aging endpoints (e.g., function, cognition, and independence).

(c) Triple-negative breast cancer (TNBC): no deterioration in HRQoL with immunotherapy

In IMPASSION031 study, patients with invasive stage II or III early TNBC who received neoadjuvant treatment with atezolizumab + nab-paclitaxel followed by doxorubicin + cyclophosphamide had significantly improved pathological complete response (pCR) vs. chemotherapy alone.[5] The study further demonstrated that the change in function and health-related quality of life (HRQoL) were similar in between arms and of the same magnitude. There was no added side-effect bother experienced by patients who received adjuvant atezolizumab. Adding atezolizumab in this curable setting improves clinical outcome and preserves the HRQoL of the patients. Although this study recruited a very selected population, this is especially important for the older cancer patients who are at higher risk of side effects and impaired HRQoL compared with the younger patients.

3.2 Advanced breast cancer:

(a) Triple-negative breast cancer (TNBC): Pembrolizumab in first-line setting

The KEYNOTE-355, a multicentre randomised controlled trial, examined the addition of pembrolizumab to chemotherapy in the first-line setting in patients with advanced TNBC.[6] Pembrolizumab + chemotherapy showed a significant improvement in progression-free survival (PFS) compared with chemotherapy alone for PD-L1-positive (CPS >10) mTNBC (9.7 vs. 5.6 months, HR 0.65, 95% CI 0.49–0.86, p=0.0012) and a trend of improvement in patients with PD-L1 CPS >1 (7.6 vs. 5.6 months, HR 0.74, 95% CI 0.61-0.90, one-sided p=0.0014). The improvement in PFS was observed regardless of chemotherapy partner. For patients aged >65, there was also a trend of improvement in mPFS in PD-L1 CPS >10 (10.7 vs. 7.6 months, HR 0.67, 95% CI 0.37-1.23). The results of KEYNOTE-355 were consistent with the phase 3 IMPASSION130 trial, which showed significantly improved mPFS with atezolizumab + nab-paclitaxel for first-line treatment of mTNBC;[7] and at the same time, offered more chemotherapy options for patients not suitable for nab-paclitaxel.

(b) HR+ Her2- advanced breast cancer: any new chemotherapy agent?

The CONTESSA trial was a randomized, phase II trial enrolling 685 patients with advanced HR+ HER2- breast cancer who received prior taxane therapy. Patients were randomized to receive tesetaxel, a novel, oral taxane with every 3 week dosing, in combination with lower dose capecitabine (1650mg/m2) versus capecitabine alone (2500mg/m2).[8] At median follow-up of 13.9 months, the combination therapy demonstrated improved PFS (9.8 vs. 6.9 months) as well as improved secondary endpoints of overall response rate (57% vs. 41%) and 24-week disease control rate (67% vs. 50%). Older adults (154 patients aged ≥65) appeared to derive similar PFS benefits as compared to younger patients (HR 0.72 in older adults vs. 0.69 in patients aged <65; of note, wide CI reported for older adults [CI 0.43-1.12] given small number of patients aged ≥65 enrolled). Adverse events were common. Neutropenia, nausea and diarrhea were the most common adverse events in the combination therapy group, with the majority of patients requiring dose reductions. This study suggests that while a potentially more convenient regimen of combination oral therapies may provide a modest PFS benefit, increased toxicity may be a concern with doublet therapy, particularly for older adults where myelosuppression may be more challenging.

3.3 Symptom control/ Survivorship

Jagsi's study compared physician and patient reports of acute toxicity during breast radiotherapy and evaluated real situation of the under-recognition of symptoms.[9] Under-recognition of at least 1 of the 4 symptoms (moderate/severe pain; pruritis; edema; severe fatigue) occurred at least once during radiotherapy for 2,933/5,510 (53.2%) of the patients. Factors independently associated with under-recognition were: younger age (<60), black or other race, conventional

fractionation, not having a supraclavicular field and being treated at an academic center. Improving symptoms detection can better support patients who are receiving radiotherapy.

Wang's study evaluated the association between adherence to a diabetes risk-reduction diet (DRRD) after diagnosis and survival outcomes following breast cancer.[10] With a median of 16 years of follow-up, women with higher post-diagnostic DRRD scores had a 17% lower risk of breast cancer-specific mortality (top vs. bottom quintile HR 0.83; 95% CI: 0.67-1.02; p =0.03) and 33% lower risk of all-cause mortality (HR 0.67; 95%CI 0.58-0.78; p<0.0001). Women who improved DRRD score from low to high, before and after breast cancer diagnosis, had a significantly lower risk of breast cancer mortality (HR 0.81; 95%CI 0.65-1.00) compared with those who consistently had lower DRRD score. This is especially important for our older breast cancer survivors as keeping a good diet not only prevent common diseases including diabetes, hypertension, and ischemic heart disease, but also improve the breast cancer-specific survival.

4. Posters relevant to older patients

The poster sessions included 18 presentations focusing on geriatric oncology related research which are summarised in Table 1. Research categories ranged from basic science to clinical trials, and topics covered included geriatric assessment, surgery, radiotherapy, and therapeutics.

Conclusion

The 2020 SABCS provided many new insights into how breast cancer care can be improved and personalized. The breast cancer community grew rapidly this year and is changing what is possible for breast cancer patients. It is our hope that through continuous investigation, engagement, and dedication, we can further precision medicine and the quality of care for older adults with cancer.

Conflicts of Interest

NB has received speaker fees from AbbVie and Pfizer and travel grants from Pfizer, Lilly and Genomic Health. The other authors declare no conflict of interest.

Author Contributions

Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review

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