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Perspectives from American Society of Clinical Oncology: translational and clinical research highlights in breast and colorectal cancers

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Advances in translational and clinical research have improved our understanding of breast and colorectal cancers, and have enabled remarkable progress in their treatment. These advances continue to be of paramount importance for breast and colorectal cancers. This report will describe and comment on the key messages from selected abstracts presented at the 50th American Society of Medical Oncology annual meeting that will impact clinical practice in the near future.

In November 1964, the recently founded American Society of Clinical Oncology (ASCO) held its first national meeting in Chicago (IL, USA). Only 51 members attended the conference. At the 2014 ASCO meeting, more than 30,000 healthcare professionals gathered together in the same city to attend this prime scientific conference. The many passionate attendees not only wanted to celebrate ASCO's 50th anniversary, but they also wanted to share the results of milestone clinical and translational research and, most notably, to consider future avenues of progress against cancer. In this report, the most significant advances in both clinical and translational research presented at the 2014 ASCO plenary session and oral abstract sessions will be discussed, specifically focusing on breast and colorectal carcinomas. Both of these are among the leading causes of cancer-related deaths. Many of the results presented significantly contribute to building a pipeline of novel treatment options. Moreover, these results will soon have an impact on clinical practice and may help medical oncologists move their research forward.

KEYWORDS

- breast cancer • clinical research • colorectal cancer
- translational research

Practice-changing results: ovarian function suppression in premenopausal breast cancer patients

The role of ovarian function suppression (OFS) during either chemotherapy or endocrine treatment for premenopausal women with early-stage breast cancer (BC) has been evaluated in two trials. Ovarian failure is a common and potentially devastating consequence of chemotherapy, especially considering that 7% of women with BC are diagnosed before 40 years of age [1]. The final results of the prematurely terminated S0230/POEMS (Prevention of Early Menopause Study) study [2] showed that the addition of goserelin to standard chemotherapy is an effective method of preserving

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fertility among premenopausal women up to the age of 49 years diagnosed with hormone receptor-negative BC. Women who received the luteinizing hormone-releasing hormone analog goserelin along with standard chemotherapy were less likely to develop premature ovarian failure (22% with chemotherapy only vs 8% with goserelin; odds ratio [OR]: 0.36, 95% CI: 0.11–1.14; $p = 0.08$) and more likely to have successful subsequent pregnancies (OR: 2.22; 95% CI: 1.00–4.92; $p = 0.05$) compared with women who received chemotherapy alone. Surprisingly, the use of goserelin was associated with an improvement in the 4-year disease-free survival (DFS; 89 vs 78% in the control group; $p = 0.04$) and overall survival (OS; 92 vs 82%; $p = 0.05$). This study adds to a set of trials investigating ovarian failure that showed the heterogeneous efficacy of ovarian protection [3].

In line with these results, joint analysis of the TEXT and the SOFT trials [4] showed that adjuvant exemestane plus OFS reduced the risk of disease recurrence compared with tamoxifen plus OFS. Overall, 27% of patients were aged ≤ 40 years, 42% were lymph node positive, 36% had a tumor size larger than 2 cm and 12% were HER2 positive. After a median follow-up of 5.7 years, patients who were assigned exemestane plus OFS had a significantly reduced risk of disease relapse compared with tamoxifen plus OFS (hazard ratio [HR]: 0.72; 95% CI: 0.60–0.85; $p = 0.0002$). Similar results were observed for the 5-year BC-free interval (HR: 0.66; 95% CI: 0.55–0.80; $p < 0.0001$) and distant recurrence-free interval (HR: 0.78; 95% CI: 0.62–0.97; $p = 0.02$). To date, no significant difference in OS has been observed. These results are in contrast with a previously published trial comparing OFS with tamoxifen or anastrozole [3]. However, long-term survival data are needed to accurately assess the impact of these two treatments.

One size does not fit all: dual HER2 blockade & gene signature in early-stage HER2-positive BC

The NeoALTTO study [5] showed that the combination of lapatinib (L) plus trastuzumab (T) nearly doubled the pathologic complete response (pCR) rate (51.3%) compared with T alone (29.5%) or L alone (24.7%). The first survival analysis showed a trend towards better DFS for patients treated with the dual blockade. The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial

investigated whether dual HER2 blockade strategy was superior to adjuvant T alone in preventing recurrences. The addition of L to T, either concurrently (L+T) or sequentially (T→L), was associated with a numerical reduction in disease recurrence at 4 years compared with T alone (86% T vs 88% L+T vs 87% T→L), but the differences were not statistically significant (L+T vs T DFS HR: 0.84; 97.5% CI: 0.70–1.02; $p = 0.048$ and T→L vs T HR: 0.96; 97.5% CI: 0.80–1.15; $p = 0.610$) [6]. Similarly, no significant differences were observed in OS. Biomarker studies are ongoing to identify a subpopulation that could benefit from dual adjuvant HER2 blockade. A gene-expression signature analysis from the CALGB 40601 neoadjuvant trial has shown that HER2-positive BC is a highly heterogeneous disease and that molecular differences may explain different patterns of response to neoadjuvant therapy [7].

The preliminary results of the CALGB 40601 study showed no significant difference in pCR rates among HER2-positive patients treated with paclitaxel plus T or paclitaxel, T and L [8]. The investigators observed that 30% of patients had luminal A tumors, 31% had luminal B tumors, 31% had HER2-enriched tumors and 5% had basal-like tumors on pretreatment samples. Moreover, there was a switch in subtype after neoadjuvant therapy and in post-treatment samples 43% of patients had luminal A tumors, 3% had luminal B tumors, 5% had HER2-enriched tumors and 2% had basal-like tumors.

The impact of germline *BRCA* mutations on treatment response in triple-negative BC patients

Triple-negative BC (TNBC) is defined as a disease subgroup that is negative for estrogen, progesterone and HER2 receptor expression with, up to now, no valid predictive biomarkers available. A correlative analysis between germline *BRCA* mutations and treatment outcome in TNBC patients [9] was performed on patients enrolled in the GeparSixto trial [10]. A total of 44 (15%) mutation carriers have been detected. The vast majority of patients were found to be *BRCA1* mutation carriers (35 patients had mutations on *BRCA1*, six patients on *BRCA2* and three on RAD50/51C). Moreover, 101 patients had a family history of BC, which suggested a genetic predisposition, and 77 did not have a germline mutation. The pCR rate, defined as no invasive and noninvasive tumor in the breast

and lymph nodes (ypT0 ypN0), increased from 40.4% in TNBC patients with no family history of BC or germline mutations to 44.3% in patients with family history only and to 54.5% for patients with germline mutations. Patients with a germline mutation and family history of BC had a pCR rate of 63.6%. The improvement in pCR rates seems to be driven by a varying sensitivity to carboplatin. The addition of carboplatin increased the pCR rate by 11.5% (OR: 1.61) in patients with no family history of BC or germline mutation, by 26.7% (OR: 3.04) in patients with a family history of BC only and by 23.2% (OR: 2.60) in patients with germline *BRCA* mutations. Survival data are needed to fully assess the risks and benefits of carboplatin in *BRCA* mutation carriers.

Similar results have been reported for metastatic TNBC. A correlative study from the TBCRC009 trial [11] investigated *BRCA1/2* mutations in over 720 TNBC patients from Sardinia, Italy. Overall, 2.9% of patients carried a germline mutation in *BRCA1* or *BRCA2*. Furthermore, the study confirmed that the occurrence of TNBC is significantly associated with *BRCA1* mutation status ($p < 0.001$), but not with *BRCA2* mutation status ($p = 0.837$). Another analysis from the same study was performed to evaluate suitable biomarkers to predict response to platinum agents [12]. Although a p63/p73 ratio of ≥ 2 and *p53* and *PIK3CA* mutations failed to predict platinum response, *BRCA1/2* carriers scored higher on homologous recombination deficiency assays correlating with *BRCA1/2* inactivation compared with noncarriers. Furthermore, in non-*BRCA1/2* carriers, responders also scored higher compared with nonresponders ($p = 0.0016$). The investigators concluded that single-agent platinum is effective in both *BRCA1/2* mutation-associated and sporadic metastatic TNBC.

Moving from translational research to practical applications: the colorectal cancer paradigm

Investigators from the CRYSTAL and OPUS trials presented updated outcome results according to tumor *RAS* mutational status in metastatic colorectal cancer patients receiving chemotherapy alone (FOLFIRI and FOLFOX in the CRYSTAL and OPUS trial, respectively) or in combination with cetuximab [13,14]. In both trials, available *KRAS* exon 2 wild-type tumors were screened for 26 mutations (new

RAS mutations) in four additional *KRAS* codons (exons 3 and 4) and six *NRAS* codons (exons 2, 3 and 4) using BEAMing technology.

In the CRYSTAL trial, extended mutational analysis was possible in 65% of patients with tumors previously classified as *KRAS* exon 2 wild-type. New *RAS* mutations were detected in 15% of the patients. In the *RAS* wild-type population, the addition of cetuximab to FOLFIRI further improved all outcome parameters analyzed. Response rate (RR) was 66 versus 38% (OR: 3.11; 95% CI: 2.03–4.78; $p < 0.0001$), median progression-free survival was 11.4 versus 8.4 months (HR: 0.54; 95% CI: 0.41–0.76; $p = 0.002$) and median OS was 28.4 versus 20.2 months (HR: 0.69; 95% CI: 0.54–0.88; $p = 0.0024$) [13,15]. Similar results, although in a smaller population, were reported in the OPUS trial [14].

Microsatellite instability (MSI) derives from deficient mismatch repair (dMMR) and represents a prognostic factor in colorectal cancer patients. The prognostic impact of dMMR was analyzed in more than 7800 stage II/III patients enrolled in 17 adjuvant trials (the ACCENT database) [16]. Prognostic analyses were limited to patients receiving surgery or 5-fluorouracil (5-FU) monotherapy, whereas correlation analyses included all patients. A dMMR was present in approximately 23% and 15% of patients with stage II and stage III colorectal cancer, respectively. A dMMR was more frequently observed in female patients, patients with a higher T stage and patients with tumors located on the right side. Among patients with stage II tumors treated with surgery alone, those with a dMMR phenotype demonstrated an improved OS (HR: 0.27; 95% CI: 0.10–0.74; $p = 0.011$) and time to recurrence (HR: 0.27; 95% CI: 0.10–0.75; $p = 0.012$). Although less pronounced, the prognostic impact of dMMR status was also observed in stage II and III patients receiving 5-FU, but statistical significance was limited to stage III patients (OS HR: 0.79; 95% CI: 0.65–0.97; $p = 0.023$, time to recurrence HR: 0.80; 95% CI: 0.66–0.97; $p = 0.025$).

The AGEO multicenter study investigated the effect of MSI in terms of relapse-free survival (RFS) in stage II and III colorectal cancer patients receiving adjuvant chemotherapy [17]. In the study, 433 MSI colorectal cancer patients were analyzed worldwide (57% stage II and 43% stage III). In univariate analysis, adjuvant chemotherapy with FOLFOX was associated with an

improved RFS (HR: 0.46; 95% CI: 0.23–0.79). By contrast, chemotherapy with 5-FU failed to show an improved RFS in this population (HR: 1.02; 95% CI: 0.60–1.73). The beneficial effect obtained with adjuvant FOLFOX remained significant in multivariate analysis (HR: 0.29; 95% CI: 0.13–0.65; $p = 0.003$), particularly in stage III patients (HR: 0.38; 95% CI: 0.21–0.69; $p = 0.0014$). A trend was only observed for high-risk stage II patients. These data reinforce the value of MSI as a prognostic factor, especially in stage II patients. The use of adjuvant FOLFOX in stage III patients with MSI seems to represent an optimal choice whenever possible. In high-risk stage II patients with MSI, a case-by-case decision balancing the prognostic impact of different factors including chemotherapy choice is still preferable.

Despite *BRAF* mutant patients being prognostically disadvantaged, a molecularly guided specific treatment is not available for this population of patients. In fact, *BRAF* mutant colorectal tumors are generally refractory to BRAF inhibitors owing to resistance mechanisms mainly activated by PI3K, EGFR and MEK abnormal expression [18,19]. However, treatment strategies with multiple inhibitions of both BRAF and other known molecular pathways responsible for resistance have proven very promising. Preliminary results of a Phase I–II trial with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, and initial findings from a Phase I trial with the BRAF inhibitor encorafenib combined with cetuximab with or without the PI3K inhibitor BYL719 seem to indicate a potentially effective and safe way to biologically tailor the therapeutic options for these patients [18,19].

Colorectal cancer in the clinic: first-line treatment options & the issue of maintenance

A decade since the launch of the CALGB/SWOG 80405 study [20], which started in 2004 when both bevacizumab and cetuximab had been approved for clinical use, Venook presented the eagerly awaited results. The trial included 1137 patients who were randomized to doublet chemotherapy (physicians' choice) plus either bevacizumab or cetuximab at standard doses. In both arms, around 75% of patients received FOLFOX as backbone treatment. Over time, the trial underwent several emendations. Initially, patients were included regarding their *KRAS* status and a third arm with chemotherapy plus both the

antiangiogenic and EGFR inhibitor was included. Later on, the focus moved to *KRAS* wild-type patients and the arm with the two biologicals was closed due to the negative results of the CAIRO2 trial. The median OS, the primary end point of the study, was similar between the treatment arms (29.0 months in the bevacizumab arm vs 29.9 months in the cetuximab arm, HR: 0.92; 95% CI: 0.91–1.17; $p = 0.34$). Similarly, median progression-free survival was also comparable (10.8 months in the bevacizumab arm vs 10.4 months in the cetuximab arm; 95% CI: 1.04; $p = 0.55$). Among those who had been exposed to FOLFOX ($n = 825$), median survival favored the cetuximab arm (30.1 months vs 26.9 months); however, the difference was not statistically different (HR: 0.9). The trend was reversed among the 252 patients treated with upfront FOLFIRI. The results emphasize that bevacizumab or cetuximab with FOLFOX or FOLFIRI offer a similar advantage, and raise the bar of median survival to an unprecedented figure of 30 months. However, the trial results have raised many questions. Does the RR differ between treatment arms? Will the extended *RAS* analysis affect the survival results? Is the combination of cetuximab and oxaliplatin always safe? Venook stated that a substantial amount of data is still pending and forthcoming analyses on the RR, extended molecular biology, and detailed information on salvage surgery and postprogression treatments will be presented in future meetings.

The opportunity to incorporate a less intensive treatment period or even a treatment-free break in the therapeutic strategy has long been debated. A less aggressive treatment course and flexible treatment duration may meet patients' need for recovery from physical and mental stress, and it may be sufficient to control the disease. Moreover, a treatment-free interval would clearly be cost saving. Nevertheless, it is still uncertain whether maintenance is needed for all patients, and the optimal low-intensity treatment after induction chemotherapy is undefined, although the combination of fluoropyrimidine with bevacizumab has been widely accepted [21]. While results of clinical studies suggest continuing antiangiogenic treatment until disease progression [22,23], randomized de-escalation trials comparing different regimens failed to define an unambiguous standard. AIO 0207 [24] investigated the role of three different maintenance strategies: capecitabine and bevacizumab ($n = 159$) versus bevacizumab alone ($n = 156$) versus observation ($n = 158$). Time to

failure of the strategy was the primary end point of the study, and defined as the time elapsed from randomization to either the second progression after maintenance and reintroduction or, in case of no reintroduction, the use of a second-line drug or no further treatment. The aim of the study was to verify the noninferiority of observation or bevacizumab alone compared with the combination arm, with a noninferiority HR limit of 1.43. Secondary end points included OS and quality-of-life assessments. While the noninferiority of bevacizumab alone compared with bevacizumab and 5-FU was demonstrated (HR: 0.98; 95% CI: 0.76–1.26), the same was not true for the observation alone arm since the HR confidence interval crossed the pre-specified boundary of 1.43 (HR: 1.22; 95% CI: 0.96–1.57). Although the rate of full chemotherapy reintroduction after disease progression was much lower than expected, the OS was similar among treatment arms (23.8 months with standard maintenance treatment vs 26.2 months with bevacizumab alone vs 23.1 months without any treatment). The results of the study confirm the value of continuing bevacizumab (with or without depotentiated chemotherapy) until disease progression and certainly underline the need for a personalized maintenance strategy.

Conclusion

Once again, the ASCO meeting offered the chance to bring together the leading results

from studies of breast and colorectal cancers. Overall, more than 2000 abstracts were selected for presentation. New and compelling data for the use of targeted therapies in breast and colorectal cancers in both adjuvant and advanced settings were presented and discussed at the plenary session. These practice-changing results are not only determining clinical advances, but are also shaping potential future developments. The international health professionals who attended the 50th ASCO Annual Meeting from around the world have learned about and commented on exciting advances. Furthermore, they have gained insight into the evolving landscape across all the relevant topics and been shown that translational and clinical research have never been so close.

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