American Society of Clinical Oncology highlights 2013: breast cancer and gynecological malignancies

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The American Society of Clinical Oncology 2013 Annual Meeting took place from May 31 until June 4 2013 in Chicago (IL, USA). Highlights within the area of gynecological oncology and breast cancer included two studies in cervical cancer addressing screening as well as treatment of advanced disease. In breast cancer, the presented studies covered a wide range of topics from local therapy to targeted therapy in the advanced setting. They were not practice changing but rather for the most part confirmatory of earlier findings. Last but not least, a positive Phase III study, BOLERO III, proved the hypothesis that trastuzumab resistance can be overcome by intracellular signal transduction using the mTOR inhibitor everolimus.

Gynecological cancers

A cluster randomized controlled trials evaluating the impact of cervical cancer screening was able to demonstrate that biannual visual inspection with acetic acid screening significantly downstaged cervical cancers (50 vs 24 ≤ stage IIB; $p = 0.002$) and decreased cervical cancer mortality (67 vs 90; hazard ratio [HR]: 0.685; $p = 0.003$). The observed 31% mortality reduction was estimated by the authors to amount to the prevention of more than 22,000 annual cervical cancer deaths in India and 72,000 worldwide [1].

In advanced primary stage IVB or recurrent/persistent cervical cancer (GOG 240), the nonplatinum doublet topotecan/paclitaxel was not able to improve survival compared with cisplatin/paclitaxel. However, the addition of bevacizumab (15 mg/kg every 3 weeks) significantly improved progression-free survival (PFS; median 8.2 vs 5.9 months; HR: 0.67; $p = 0.0002$) as well as overall survival (OS; median: 17 vs 13.3 months; HR: 0.71; $p = 0.0035$). There were significant differences favoring the chemotherapy-only arm for gastrointestinal and genitourinary fistulas, hypertension, neutropenia and thromboembolism [2]. Given these mostly numerically low but significant differences in side effects, more extensive data analysis will hopefully be able to elucidate which patients derive particular benefit from the antiangiogenic regimen.

In ovarian cancer patients without progression after first-line chemotherapy, the AGO-OVAR 16 trial evaluated the impact of a 24-month maintenance therapy with pazopanib [3]. The study met its primary end point with pazopanib significantly prolonging PFS (median 17.9 vs 12.3 months; HR: 0.76; $p = 0.0021$). After a median observation time of 24 months, only approximately 20% of the events needed for OS analysis had been observed. There was an increase in several grade 3–4 side effects with pazopanib versus placebo consistent with tyrosine-kinase inhibitor therapy. Given the maintenance data for bevacizumab from ICON 7 [4] and GOG 218 [5], the overall therapeutic ratio (benefit vs side effect) will certainly decide whether, and if so which, maintenance therapy is suitable for an individual ovarian cancer patient after first-line chemotherapy. In particular, considering the potential toxicities, a biomarker-based therapy approach would certainly be preferable.

Early breast cancer

Two studies in locoregional therapy addressed axilla management: the NSABP and AMAROS trials. Long-term results of NSABP-B32 confirm the modern standard of sentinel-lymph node biopsy in a randomized comparison to axillary lymph node dissection (AD). In 3986 clinically node-negative patients, only 81 (sentinel lymph node biopsy) versus 84 relapses (AD) were

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detected (HR: 0.96; $p = 0.77$). After 10 years, immunohistochemical detection of occult tumor cells (616 out of 3268) did not have an impact on OS and was, thus, not recommended by the authors [6]. The EORTC AMAROS trial randomized patients with positive sentinel nodes to subsequent AD versus lymph node radiation. In 67.1% of patients no further involved lymph nodes were detected after AD. Local relapse rates after 5 years were very low in both arms at 0.43 (AD) and 1.19% (radiation), respectively, and OS did not differ (HR: 1.17; $p = 0.34$). Whereas AD was associated with more lymph edema even after 5 years (28 vs 13%; $p > 0.0001$), radiation therapy led to a trend in impaired arm mobility [7]. The authors concluded that radiation treatment could be considered standard in cases of positive sentinel lymph nodes. However, given the recent change of axillary management in forgoing AD in selected patients with one to two involved sentinel nodes, the collective for whom the AMAROS results can be directly applied to seems rather small.

The question of avoiding overtreatment by adjuvant chemotherapy in luminal tumors was addressed by a common analysis of ABCSG-8 and transATAC tumors using the PAM50 assay. In patients with one to three involved lymph nodes ($n = 543$; all endocrine responsive), PAM50 was able to identify a low-risk group with a 10-year metastasis-free survival of less than 10%. In total, 71% of patients with one lymph node had a luminal A tumor and an 8.4% 10-year metastasis-free survival [8]. These data underline the importance of current trial concepts, such as WSG-ADAPT, which tries to spare patients with zero to three lymph nodes from chemotherapy if they have a low or intermediate Oncotype DX® (Genomic Health, Inc., CA, USA) score and a good proliferation response to a 3-week preoperative endocrine therapy [101].

The use of carboplatin area under the curve 1.5 weekly in addition to an anthracycline–taxane containing neoadjuvant therapy improved the pathological complete remission (pCR) rate (46.7 vs 37.2%) in the GBG-AGO-B Geparsixto-trial, particularly in triple-negative tumors (pCR rate 58.7 vs 37.9%). However, it was associated with increased toxicity [9].

In HER2-positive disease, the Alliance C40601 trial showed that dual blockade (trastuzumab plus lapatinib) with a backbone of 16 weeks of paclitaxel, improved pCR compared with single blockade trastuzumab versus lapatinib numerically, although not statistically (pCR breast: 56 vs 46 vs 37%, respectively) [10].

The ACOSOG Z1041 Phase III trial did not see a difference in pCR rates after neoadjuvant four-times fluorouracil, epirubicin and cyclophosphamide – 12-times paclitaxel depending on whether trastuzumab was already started with the anthracycline or only with the taxane (in breast pCR: 56.5 vs 54.2%, respectively; $p = 0.72$) [11]. These data do not support routine use of trastuzumab concurrent with anthracyclines in the neoadjuvant setting. Last but not least, survival analysis of the NOAH trial confirmed the significant benefit from neoadjuvant trastuzumab (event-free survival [EFS] HR: 0.64; $p = 0.016$; OS HR: 0.66; $p = 0.055$). Interestingly, EFS in HER2-positive disease without trastuzumab was worse than that of HER2-negative disease (62 out of 118 vs 45 out of 99). pCR under trastuzumab was significantly correlated with improved EFS (HR: 0.17; $p < 0.0001$). Cumulative congestive heart failure grade III rate was 2.1% after 5 years in the trastuzumab arm [12].

In endocrine-sensitive disease, the ATTom trial ($n = 6953$) confirmed the advantage of 10 versus 5 years of tamoxifen (response rate [RR]: 0.85; $p = 0.003$). As seen in the ATLAS trial, the benefit in relapse-free survival was particularly visible after the first 5 years and continued to persist for more than 15 years. The decrease in breast cancer-related deaths was visible after about year 7 (RR: 0.88; $p = 0.06$) and amounted to an approximately 3% absolute benefit at year 15. Prolonged tamoxifen therapy was associated with an increase in endometrial cancers (102 vs 45) and related deaths (37 vs 20) with an absolute risk of approximately 0.5%. Taken together, the ATLAS and aTTom trials ($n = 17,477$) demonstrate a significant benefit regarding breast cancer-related deaths (RR: 0.85; $p = 0.001$) and overall mortality (RR: 0.91; $p = 0.008$) for 10 versus 5 years of tamoxifen [13]. Current AGO guidelines already recommend 5–10 years (depending on risk and tolerability) of endocrine therapy in early breast cancer with tamoxifen in premenopausal and a sequence of tamoxifen and aromatase inhibitors in postmenopausal patients [102].

Therapy in metastatic breast cancer

In primary breast cancer, uPA and PAI-1 are ASCO-recommended prognostic biomarkers for node-negative disease. Recent 10-year long-term follow-up of the prospective Chemo N0 trial validated these prognostic markers at highest level of evidence according to the criteria by [14] and demonstrated that uPA/PAI-1 high-risk

patients benefit substantially from adjuvant chemotherapy [15]. For the first time, an oral uPA inhibitor, WX 671 (upamostat), was evaluated in breast cancer. In the first-line setting, there was no significant benefit from adding WX671 to capecitabine in an unselected patient population. In the exploratory analysis, patients with prior adjuvant chemotherapy seemed to benefit with a median PFS of 8.3 versus 4.3 months. There were no toxicities beyond those expected for capecitabine [16]. At ASCO 2010, WX671 was associated with prolonged survival in pancreatic cancer when combined with gemcitabine chemotherapy [17]. Further evaluation of the anti-uPA therapy – preferably in a biomarker-guided trial concept – seems promising.

The highlight of the metastatic breast cancer sessions was the first presentation of the BOLERO-3 results regarding addition of everolimus to trastuzumab and vinorelbine after trastuzumab failure. The study met its primary end point by improving median PFS from 5.78 to 7 months (HR: 0.78; $p = 0.0067$) by adding 5 mg/day of everolimus. This was associated, however, with an increase in toxicities such as stomatitis, rash, diarrhea and fatigue but not a decrease in quality of life compared with the control arm [18]. BOLERO-3 demonstrates for the first time that mTOR inhibition may overcome trastuzumab resistance. However, considering the small PFS benefit and the added toxicity, the actual clinical impact of this therapy concept will still need to be determined, in particular once T-DM1 becomes available internationally. Nevertheless, the fact that the number of

effective anti-HER2 therapy options is constantly increasing is good news for our patients.

Conclusion

Similar to last year, this year's ASCO confirmed a number of therapy concepts in breast cancer without immediately requiring changes to our current guidelines or everyday clinical practice. Another highlight of the breast cancer sessions was the David A Karnofsky Lecture, which is associated with ASCO's highest clinical award and this year was held by Martine Piccart (Breast International Group; Brussels, Belgium). Piccart, who was honored for her international trial network, Breast International Group, described the past and future of academic clinical trials and the resulting impact on breast cancer management in her visionary talk. The Karnofsky lecture, together with all the other interesting talks and posters can be seen in the ASCO Virtual Meeting [103].

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