Selected literature

Monika Dudzisz-Śledź, Piotr Wysocki

The updated recommendations of ASCO and CCO for use of bone modifying agents in patients with breast cancer and bone metastases

The updated recommendations of ASCO (the American Association for Clinical Oncology) and of CCO (Cancer Care Ontario) concerning the use of bone modifying agents (BMA) in metastatic breast cancer (mBC) patients were published in the Journal of Clinical Oncology in October 2017. The modifications of the recommendations are mostly based on the recently published results of phase III studies and concern the intervals between the consecutive doses of BMA and the role of MA in pain control.

According to recommendations, patients with breast cancer with bone metastases should receive BMA. The available options are denosumab (administered in dose of 120 mg, subcutaneously every four weeks), pamidronic acid (in dose of 90 mg, intravenously, every 3–4 weeks), and zoledronic acid (administered intravenously in a dose of 4 mg every 12 weeks or every 3–4 weeks). In conformity with recommendations, none of these agents overweight the others. The analgesic activity of BMA is limited and these agents should not be used only to control the pain. In the therapy of pain related to bone metastases in breast cancer patients, it is recommended to adhere to actual standards: analgesic drugs, radiotherapy, surgical procedures, systemic anticancer therapy, and supportive care, or these patients should be monitored by centres dedicated to providing pain control.

Comments

The updated recommendations of ACSO and CCO systematise the issue of the time intervals between the administrations of zoledronic acid in patients with breast cancer with bone metastases. Based on the results of the phase III clinical trials published during the last year, an equivalent activity and safety of use of zoledronic acid in standard dose of 4 mg IV every 4 or 12 weeks was proven. The current recommendations clearly suggest the possibility to dose the zoledronic acid once per three months from the very beginning of the therapy based on this bone modulating agent.

A second important aspect of these recommendations is the evidence of no clear advantage of denosumab over zoledronic or pamidronic acid, concerning the clinical activity and safety. In the context of the actual limitation of the reimbursement of denosumab, this information is especially important because it may ensure breast cancer patients that administration of zoledronic or pamidronic acid constitute an optimal prevention of skeletal-related events (SRE).

Source

1. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: An American Society of Clinical Oncology–Cancer Care Ontario focused guideline update. J Clin Oncol. 2017; 10. doi: 10.1200/JCO.2017.75.4614.

Translation: dr n. med. Aleksandra Hołowiecka
Oncology in Clinical Practice 2017, Vol. 13, No. 6, 316–319. DOI: 10.5603/OCP.2017.0042, copyright © 2017 Via Medica, ISSN 2450–1654

Piotr Wysocki

San Antonio 2017. The EBCTCG — meta-analysis — clear benefit of dose-dense adjuvant chemotherapy, especially in sequential schedules

During the 40th Breast Cancer Conference the results of the EBCTCG-meta-analysis were presented showing the benefit of the dose-dense adjuvant chemotherapy (ddAC, ddEC) and of the schedules containing the sequence of anthracyclines and taxanes. The meta-analysis involved individual data of 10,000 patients enrolled into seven clinical trials comparing the dose-dense chemotherapy (every two weeks) with a standard dose (every three weeks) and of 11,500 patients enrolled into nine clinical trials comparing the sequential schedules anthracyclines and then taxanes with concurrent use (anthracyclines + taxanes). After one year of observation the use of dose-dense chemotherapy compared to standard chemotherapy, resulted in a decrease by 17% of relapse risk and by 15% of death risk. On the other hand, the sequential chemotherapy compared to concurrent use of anthracyclines and taxanes was associated with a significantly decreased relative risk of relapse — by 13% and of death — by 11%. The significant benefits of the more intensive chemotherapy and of the sequential administration of anthracyclines and taxanes was observed in the case of ER-positive and ET-negative breast cancer. In this meta-analysis no differences were shown concerning the safety or late side effects between the dose-dense vs. standard chemotherapy.

Comments

The results of the EBCTCG analysis clearly show that the shortening of the intervals between the anthracycline-based chemotherapy cycles (AC, EC), as well as a sequential use of anthracyclines and taxanes, significantly decreases the risk of relapse of the disease and of patient's death. Based on these results, we should clearly ascertain that the concurrent administration of anthracyclines and taxanes **should not be used in clinical practice**. On the other hand, the chemotherapy based on anthracyclines with shortening of the intervals between the chemotherapy cycles (ddAC, ddEC) is a valuable and safe therapeutic option, which should be applied especially in the case of patients with high risk of disease reoccurrence.

Source

1. Gray R, Bradley R, Braybrooke J, et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. San Antonio Breast Cancer Symposium. 2017. 6 Dec 2017.

San Antonio 2017. Ribociclib in combination with endocrine therapy (goserelin + tamoxifen/aromatase inhibitor) — showed efficacy in premenopausal women with advanced breast cancer

A total of 672 premenopausal patients with advanced, metastatic breast cancer were enrolled into the phase III MONALEESA-7 trial. The median age of patients was 43 years (ribociclib-HTH) and 45 years (placebo-HTH). In the ribociclib arm 87 patients received tamoxifen and 248 — AI, while in the placebo arm it was 90 and 247, respectively. More than 56% of patients had visceral metastases and 23–24% had only bone metastases. The use of ribociclib was associated with a decrease of the relative progression risk by 45% (HR = 0.553, 95% CI 0.441–0.694), with no evident difference between tamoxifen HR = 0.58 and AI HR = 0.57 arms. In the ribociclib arm a significantly higher objective response rate was observed — 40.9% *vs.* 29.7% (50.9% *vs.* 36.4% in patients with measurable metastases). Clinical benefit (CR, PR, SD) was observed in 80% and 67% of patients in the ribociclib and placebo arms, respectively. In the ribociclib arm the adverse events were associated with a four-times higher probability of therapy break and six-times higher risk of dose reduction. The most frequent side effects in CTCAE grade 3–4 were neutropaenia (60.6% — ribociclib *vs.* 3.6% — placebo), anaemia (3.0% *vs.* 2.1%), tiredness (1.2% *vs.* 0%), diarrhoea (1.5% *vs.* 0.3%). The evaluation of the quality of life according to the EORTC QLQ-C30 protocol showed significantly better, clinically important parameters in the ribociclib arm.

Comments

The MONALEESA-7 study clearly showed the activity of ribociclib (CDK4/6 inhibitor) in hormone-dependent breast cancer in premenopausal women, and the activity of ribociclib in combination with selective modulator of oestrogen receptor — tamoxifen, as

shown for the first time. This study also confirms the validity of the EMA decision to register CDK4/6 inhibitors in combination with endocrine therapy (AI or tamoxifen) in premenopausal women provided that efficient, pharmacological suppression of ovaries is also used.

Source

1. Tripathy D, Sohn J, Im S-A, et al. GS2-05. First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA-7 trial. San Antonio Breast Cancer Symposium 2017. 6 Dec 2017.

San Antonio 2017. Adjuvant trastuzumab did not improve outcomes for patients with HER2 low breast cancer

A total of 3,200 patients with HER2 low (IHC 1+, 2+ without amplification) breast cancer with feature N+ (high-risk group) or N0 were enrolled into a randomised phase III NSABP B-47 trial. In the adjuvant therapy, patients received standard chemotherapy 4 × AC → 12 PXL or 6 × TC and then were randomised to receive, or not, 12 months of trastuzumab maintenance therapy. After a median follow-up of 46 months, it was proven that administration of trastuzumab compared to a standard maintenance therapy was not associated with any additional benefits. The five-year disease-free survival rate (DFS) was 89.6% and 89.2% in the trastuzumab and control arms, respectively (HR = 0.98, p = 0.09), and five-year overall survival rates (OS) were 94.8% and 96.2%, respectively (HR = 1.33, p = 0.14)

Comments

A hypothesis that breast cancer patients with expression (but not overexpression) of HER2 may also benefit from trastuzumab was based on a retrospective analysis of subgroups from the registration study of trastuzumab — used in maintenance therapy (NSABP-B31 and N9831). In effect, a NSABP B-47 trial was designed and conducted, which aimed to test this interesting hypothesis. No benefits of trastuzumab after adjuvant chemotherapy in breast cancer patients without amplification of *HER2* (FISH < 2.0) or without overexpression of HER2 (IHC 1+, 2+) acknowledges that the actual standard of adjuvant therapy constitutes an optimal management.

Source

1. Fehrenbacher L, Cecchini RS, Geyer CE, et al. GS1-02. NSABP B-47 (NRG oncology): Phase III randomized trial comparing adjuvant chemotherapy with adriamycin (A) and cyclophosphamide (C) weekly paclitaxel (WP), or docetaxel (T) and C with or without a year of trastuzumab (H) in women with node-positive or high-risk node-negative invasive breast cancer (IBC) expressing HER2 staining intensity of IHC 1+ or 2+ with negative FISH (HER2-Low IBC). San Antonio Breast Cancer Symposium, 6 December 2017.

San Antonio 2017. New data concerning nab-paclitaxel in breast cancer therapy

During the general session, two interesting reports, which had evaluated the long-term survivals of patients and which had broadened our knowledge concerning the role of nab-paclitaxel in breast cancer therapy, were presented. The first study (GeparSepto) concerned preoperative chemotherapy with use of nab-paclitaxel and a CALGB40502/NCCTG N063H trial involving the activity of nab-Paclitaxel in the treatment of generalised breast cancer.

The analysis of GeparSepto study concerned patients with triple-negative breast cancer (TNBC) and with hormone-dependant breast cancer (HR+). The patients received preoperatively 12 courses of paclitaxel or of nab-paclitaxel (125 mg/m^2) and then 4 × EC. The use of nab-paclitaxel significantly increased the overall pathologic responses rate by 9% (from 29% to 38%) and in the case of TNBC from 26% to 48%. The survival analysis, conducted after 49 months of observation showed a significant decrease in the relative relapse risk by 31% (HR = 0.69, p = 0.0044) with the four-year disease free survival rates (DFS) reaching 83.5% and 72.8% for nab-paclitaxel and paclitaxel, respectively.

In the CALGB40502/NCCTGN063H trial, 799 patients with generalised breast cancer were randomised to three arms: nab-paclitaxel 150 mg/m^2, paclitaxel 90 mg/m^2, or ixabepilone 16 mg/m^2 (n each arm chemotherapy was administered every week 3 times with one week interval). All patients were also receiving bevacizumab. In the presented analysis, no significant difference in the disease progression-free survival (PFS) between nab-paclitaxel and paclitaxel, was shown. On the other hand, paclitaxel proved to be significantly more efficient than ixabepilone. Concerning the OS, the median OS in the paclitaxel arm was 27.1 months,

in the nab-paclitaxel arm 24.2 months, and in the ixabepilone arm 23.6 months. A significant difference in OS was shown only between the paclitaxel and ixabepilone arms. In the analysis of subgroups, concerning PFS and OS, a trend to higher activity of nab-paclitaxel in TNBC and of paclitaxel in HR+ breast cancers was proven.

Comments

The presented studies show the activity of nab-paclitaxel in the treatment of breast cancer patients. However, they do not provide clear evidence for a general advantage of this drug over the classic paclitaxel used in a weekly schedule. In the case of the generalised breast cancer, in first-line therapy standard paclitaxel is definitely not worse than nab-paclitaxel, especially when administered in HR+ breast cancer patients.

Concerning the preoperative therapy, the use of nab-paclitaxel is associated with higher rates of pCR and with decreased relapse risk compared to standard paclitaxel. The subgroup analysis should be emphasised because it showed that in patients in whom a pCR had been achieved, no difference in OS and DFS between the nab-paclitaxel and paclitaxel arms was observed. However, the difference of DFS in favour of nab-paclitaxel emerges in the case of patients who did not achieve pCR. To sum up, in clinical practice, in palliative therapy, standard paclitaxel in a weekly dosage is an active schedule. On the other hand, in patients who do not achieve pCR after a preoperative chemotherapy containing paclitaxel weekly, especially in the case of TNBC breast cancer, we should consider an adjuvant therapy. In these patients, the administration of capecitabine seems to be an optimal approach according to the results of the CRAETE-X study.

Sources

1. Schneeweiss A, Jackisch C, Schmatloch S, et al. Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline/cyclophosphamide for patients with early breast cancer — GBG69. San Antonio Breast Cancer Symposium, December 5–9, 2017. Abstract GS3-05. abstracts2view.com/sabcs/view.php?nu=SABCS17L_943&terms=].
2. Rugo HS, Barry WT, Moreno-Aspitia A, et al. GS3-06. Long-term follow-up of CALGB 40502/NCCTG N063H (Alliance): A randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-Paclitaxel (NP) or ixabepilone (IX) +/– bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer (MBC). San Antonio Breast Cancer Symposium, 7 December 2017.
3. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. New Engl J Med. 2017; 376: 2147–2159. DOI: 10.1056/NEJMoa1612645.

San Antonio 2017. Trastuzumab in combination with pembrolizumab is a potentially promising approach in patients with HER2 breast cancer resistant to anti-HER2 therapy

Fifty-eight patients with HER2-positive breast cancer, and who had failed a trastuzumab or TDM-1 based therapy, were enrolled into a phase Ib/II clinical study. The primary end-point of the study was the overall response rate (ORR). In phase Ib of the study the patients with PD-L1-positive tumours received one of two doses of pembrolizumab (2 mg/kg or 10 mg/kg) + trastuzumab in three-week cycles. In phase II a pembrolizumab was used in a dose of 200 mg + trastuzumab every three weeks. The ORR in the phase Ib was 17% and in phase II was 15% (PD-L1+) as well as 0% (PD-L1–). In the group of PD-L1+ patients the median of the disease control time (DCR-CR, PR, SD) was 11.1 months and the median of response duration 3.5 months. The 12-month rate of disease progression-free survival reached 13% (PD-L1+) and 0% (PD-L1–), and the 12-month overall survival rate was 65% and 12%, respectively. The presence of the lymphocytic infiltrations in the tumour stroma (stromal TIL-sTIL) was related to a better response rate and better control of the disease. In 41% of PD-L1+ patients the presence of the lymphocytic infiltrations > 5% sTIL was detected. In the case of patients PD-L1+ with sTIL ≥ 5% the ORR equalled 39% and DCR 47%. In patients with infiltration sTIL < 5% the ORR/DCR equalled 5%.

Comments

The PANACEA study shows a potential activity of immunotherapy in HER2-positive breast cancer patients who have failed a previous anti-HER2 therapy. Several preclinical trials indicate the role of immunological mechanisms in the development of resistance to anti-HER2 therapy related to the activation of checkpoints. The presented results suggest the validity to design and conduct a phase III clinical study that would compare the combination of anti-PD-1 + anti-HER2 therapy to the actual clinical practice in patients selected in terms of biomarker (sTIL).

Source

1. Loi S, Giobbe-Hurder A, Gombos A, et al. GS2-06. Phase Ib/II study evaluating safety and efficacy of pembrolizumab and trastuzumab in patients with trastuzumab-resistant HER2-positive metastatic breast cancer: Results from the PANACEA (IBCSG 45-13/KEYNOTE-014) study. San Antonio Breast Cancer Symposium 2017. 6 Dec 2017.