Abstract

GUIDANCE BASED SUMMARY OF EVIDENCE-BASED MANAGEMENT OF PRIMARY AND METASTATIC BREAST CANCER. 21 Nov 2014.

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Background:
The global breast cancer incidence has almost tripled during a 30 years time period from 1980 to 2010, an increase from some 600 000 in individuals to 1,6 million contracting breast cancer on an annual basis, respectively. [1] Modern management includes separation of breast cancer into at least four distinct entities based on their gene expression, signatures/sequence-based characteristics, or cheaper and modified methods making these determinations, using a combination of the immunohistochemical expression of ER, PR, HER2 and proliferation together with analyses of the histological grade. [2]

Neoadjuvant therapy:
In a Cochrane analysis including 14 eligible studies, including 5 500 women, pre-operative therapy compared with post-operative therapy was not associated with a survival difference. Neoadjuvant therapy was associated with a statistically increased risk of local relapse if surgery plus minus radiotherapy was not included as therapy modalities. [3] Further analyses of this study revealed that patients not responding to 2 courses of TAC and that were randomised to an alterative regimen containing vinorelbine and capecitabine, had a statistically significantly improved disease-free survival compared to if they continued the same type of therapy. [4] In more recent meta-analyses, including 12 bigger neoadjuvant studies with a total of 12 993 patients, the author found that patients obtaining a pathological complete remission (pCR) had a statistically significantly higher likelihood of obtaining long-term survival. [5] In two studies, NeoALTTO and NeoSphere, the addition of one more anti-HER2 agent, lapatinib and pertuzumab, respectively, increased the pCR-rate with almost a factor 2 or slightly more in both studies, although the effect was not as marked with the combination of trastuzumab and lapatinib. [6], [7] Patients with a HER2-positive disease receiving trastuzumab had a 50 % likelihood of obtaining a pCR. Patients with so-called triple negative cancer had a 34 % likelihood of obtaining a pCR, while patients with a hormone receptive cancer graded as 1 or 2 had only 7 % chance of obtaining pCR[5].

Adjuvant endocrine therapy:
Adjuvant endocrine therapy to an ER-positive patient results in almost 13 % absolute 1-3 reduction in the risk of recurrence, patients having an ER-negative and PR-positive disease had no benefit as well as patients with a ER-negative and PR-positive disease. Patients with an ER-positive and PR-positive disease had a similar gain as patients with ER and PR-positive disease. [8]

In the head-to-head comparisons, 5 years of tamoxifen versus aromatase inhibitor , the aromatases improves the relapse-free survival with about 4 % at 5 years of follow-up, but so far with no improvement of overall survival. [9].

Longer duration of endocrine therapy is beneficial; in the first published study five years of tamoxifen followed by some further years of the aromatase inhibitor resulted in a statistically significant survival improvement for the node positive group as well as improvement for five additional years. [10], [11] Furthermore, a meta analysis of 3 smaller studies, the Scotish study, NCBP, ECCO and the larger studies ATLAS and aTTom together resulted overall in a reduction in breast cancer mortality. [12] + Gray R unpublished data

Adjuvant chemotherapy:
Based on some 100 000 randomised patients (45 000 to taxane-based regimens, 22 000 to anthracycline-based regimens, 31 000 to poly chemotherapy regimens and 5 000 patients to more or less of anthracyclines. [13]
In short, the *relative reductions* in recurrence- and breast cancer survival improvements are similar irrespective of age, ER-status, nodal status or tumour grades or tumour size. The absolute risk reduction is more obvious for patients with a higher risk compared with patients at a lower risk stratum, e.g a small luminal A like cancer with low risk has in practice no significant benefit by adding chemotherapy to the endocrine therapy. [13]
The St Gallen guidelines from 2013 includes therapy recommendations for the immunohistochemical based groupings of breast cancer, aiming at giving endocrine therapy to ER-positive patients without adverse factors and chemotherapy to patients with adverse tumour factors, plus/minus anti-Her-2 based therapy and or endocrine therapy. [14]

Dose dense therapy:
Dose dense therapy with different designs and strategies have been analysed in 10 trials. The disease-free and overall survivals were improved with dose dense regimens compared with standard regimens. [15]

Adjuvant anti-HER2 based therapies:
Several prospective and randomised studies have demonstrated survival gains by adding trastuzumab to chemotherapy, either in sequence or concurrently, the latter seems to be more effective. [16], [17], [18] . The Slamon study BCIRG 006 included an anthracycline-free regimen, although that arm had numerically more relapses compared with the antracycline-based arm, having more secondary leukaemias/MDS and cardiac side effects.
Two years of trastuzumab is not better than one year [17], and there are on-going studies investigating less than one year of therapy. So far, however, no data confirms the similar efficacy as the standard therapy of one year of trastuzumab. [19] . In the ALTTO-study, 8 381 patients were randomised in a 4-armed study, the overall survival was statistically significantly worse for the lapatinib arm alone (HR 1.36, 95%, KI, 1.09-1.72) despite that these patients received one year of trastuzumab in addition, based on the datafrom the interim analysis (Perez et al., ESMO 2014). The two combined arms with trastuzumab and lapatinib tended to be slightly "better" compared with trastuzumab alone, although not statistically significant (Perez et al., ESMO 2014)

Adjuvant bisfosfonates:
Individual data from 17 719 women was analysed. For the postmenopausal women a reduction in skeletal recurrences were noticed, as well as a reduction in breast cancer mortality by 17 %, although for some reason no effect was seen for the premenopausal group. (Coleman et al., SABCS 2013).

Metastatic breast cancer:
Some institutions have described marked improvements in survival for metastatic disease, while other population-based materials have failed to demonstrate any overall improvement in overall survival for metastatic disease, except for the younger individuals. [20]

Two prospective studies have demonstrated that by taking a biopsy from a radiological or clinical suspected metastatic lesion, you change management in 1/6-1/7 patients. [21], [22] Many retrospective studies have demonstrated lack of stability for standard markers like ER and PR (and to a lesser extent HER-2) in recurrent breast cancer, compared with the content in the primary cancer. [23], [24] Some data indicate that given adjuvant therapies may influence the marker alterations. [24] Based on these prospective and retrospective findings, a biopsy of recurrent breast cancer is recommended in the updated guidelines from the consensus conference of advanced breast cancer. [25]

Patients with isolated local or loco regional recurrences should be treated firmly aiming at obtaining long-term survival by performing a combination of local therapy modalities and the use of systemic therapies based on the tumour characteristics. However, for the vast majority of the breast cancer patients, recurrence – systemic metastatic breast cancer - is a chronic disease requiring repeated tailored interventions based on the tumour characteristics. [25] In short, patients with visceral disease and with signs of rapid progression, in particular those with short relapse-free intervals should be treated with upfront chemotherapy if HER2-positive, anti HER2-based therapy should be added.

Anti-HER2 based therapies in the metastatic setting:
The combination of pertuzumab, trastuzumab and chemotherapy should be offered as first-line therapy of a verified HER2-positive metastatic disease, while the triple combinations adds almost 16 months in median survival prolongation. [26], [25] Upon further progression of HER2-positive disease, a dual blockade of trastuzumab plus lapatinib results in an overall survival gain versus lapatinib alone with 4,5 months. [27]
The use of trastuzumab emtansine compared with lapatinib capecitabine result in a 5,8 months median survival gain for the former regimen. [28]
It is generally agreed that patients progressing on HER2-based therapy, should be offered different types of HER2-based therapies by changing the chemotherapy backbone or by using the viable anti-HER2 agents. The evidence for these strategies is described in this short abstract, based on the data from the randomised studies, but there are still a lot of studies to be carried out in order to have full evidence of all these activities presently partly performed in the clinical management of breast cancer patients.

Other targeted agents for metastatic breast cancer:
Standard endocrine therapies, aromatase inhibitors and tamoxifen are of course the corner stone for patients with more indolent and verified ER expression [25].
The combination of everolimus and examestane versus examestane alone, for patients with ER-positive disease, who had progressed on initial lestrozole or anastrozole therapy, resulted in a clinically meaningful improvement in progression-free survival for the combination arm with 4,6 months, but no statistically significant overall survival gain was recorded, although numerically it was a gain with a few months. [29]

More recently, the addition of the CDK4/6 inhibitor palbociclib to letrozole versus letrozole alone, resulted in rather marked improvement in progression-free survival, but so far no overall survival gain has been demonstrated (Finn et al., AACR 2014). This is a new and promising strategy, but further studies are needed. Proper research strategies are needed aiming at finding therapy predictive markers for CDK4/6 inhibition, as well as for blockade of mTOR and similar up- and down stream targets like PI3K and AKT.

Anti-angiogenic therapy:
Anti-angiogenic therapy is theoretically a highly interesting therapy approach for management of cancer, including breast cancer. However, the use of adjuvant bevacizumab and the use in the metastatic setting have not resulted in major achievements, and no significant overall survival gains have so far been observed in the metastatic setting. Similarly, other compounds with anti-angiogenic capacities, like sunitinib and sorafenib, have not resulted in improvements in progression free- and overall survival, despite that marked increases in tumour response have been observed. [30], Baselga et al., ESMO 2014

Conclusion:
Neoadjuvant and adjuvant management of breast cancer is aiming at curing patients. Therapy should be selected based on risks and tumour marker signatures. Breast cancer is a very heterogeneous disease, and accordingly combination therapies have frequently been demonstrated to result in improved outcomes, i.e. the combination of chemotherapy and endocrine therapy and the combination of chemotherapy and anti-HER2 based therapies.

Management of recurrent breast cancer should be aiming at improving survival with a maintained and improved quality of life. This can normally be obtained by carefully analysing the clinical and tumour biological factors, aiming at tailored therapy approaches based on the tumour characteristics.

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