Systemic chemotherapy regimens in early breast cancer patients: updated recommendations from the BSMO breast cancer task force

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SUMMARY

Since the publication from the Belgian Society of Medical Oncology breast cancer task force in 2014 in the Belgian Journal of Medical Oncology, new information has become available on optimal chemotherapy regimens for early breast cancer patients. On February 24th, 2017, 37 medical oncologists involved in breast cancer management reviewed the most important scientific data on this topic. The authors of this paper summarised the findings, and sent a questionnaire to the members asking for their input. This paper summarises the consensus of this exercise.

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INTRODUCTION

Adjuvant chemotherapy in early breast cancer improves overall survival, but it is associated with considerable short- and long-term toxicities as well as impact on quality of life.[1] Deciding whether a patient with early breast cancer requires chemotherapy is a first important step. Gene expression profiles have been developed and some of them have recently been validated.[2] Level I evidence is now available that these tests may help in deciding on whether to prescribe adjuvant chemotherapy or whether we may spare chemotherapy use and its associated discomfort in a significant proportion of patients. However, when the choice for chemotherapy is made, the second difficult decision is which chemotherapy regimen to use.

The Belgian Society of Medical Oncology (BSMO) breast cancer task force already published on this topic in 2014.[3] Because of newly reported data, the task force discussed this issue again in depth at the annual BSMO meeting on Febru-

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TABLE 1. Possible (NEO)ADJUVANT chemotherapy regiments.

Setting	HER2 neg ER pos	Triple neg	HER2 pos
Possible chemo-regimens	4xEC ➔ 12xPac qw 4xECdd ➔ 12xPac qw 3xFEC ➔ 3xDoc 6xTC (pN0 or pN1) 4xTC (elderly or lower risk)	4xECdd ➔ 12xPac qw 4xEC ➔ 12xPac qw 4xECdd ➔ 12xPac+Carbo(AUC2), (certainly an option if BRCA+, only data in neoadjuvant setting) 3xFEC ➔ 3x Doc 6xTC (pts at cardiac risk) 4xTC (elderly)	4xEC ➔ 12xPac+Trast 6xTCarboH 3xFEC ➔ 3xDoc+Trast 4xTC+Trast (elderly or low risk) 12xPac+Trast (elderly or low risk) Pertuzumab (P) can be combined with Trast in adjuvant or neoadjuvant setting in high risk patients* Possible regimens: 4xEC ➔ 12xPac+Tras+P 6xTCarboH-P 3xFEC➔3xDoc+Trast+P

E=epirubicine, C=cyclophosphamide, Carbo=carboplatin, Pac=paclitaxel, Doc or T =docetaxel, Trast or H=trastuzumab, P=pertuzumab, F=fluorouracil.
*Pending EMA approval and reimbursement.

ary 24th, 2017 in Brussels, with 37 attending Belgian medical oncologists. No systematic literature search was performed, but all relevant known publications and abstracts (expert opinion) on this topic were integrated. The four authors of this paper summarised the discussion after the meeting, and constructed a new recommendation table and a questionnaire. This table and questionnaire were sent to the 37 attending oncologists, and fourteen (38%) oncologists returned the completed questionnaire. When a certain statement/change was not accepted by more than half of the respondents, the change was not accepted, and the summary was altered in consequence. Finally, the four authors reassembled all information, and prepared a final overview table (*Table 1*).

Several decisions were taken when preparing this table: 1) the mentioned regimens are not the only possible adjuvant or neoadjuvant regimens available/possible, but are the most commonly used schemes in Belgium; 2) adjuvant and neoadjuvant regimens were integrated in one table. Although the evidence for specific regimens differs for the adjuvant and the neoadjuvant setting, there is no strong biological reason to use different schemes in both settings; 3) there is no priority for the different regimens proposed for each specific setting; there may be individual reasons to prefer one of these possibilities over others depending on the clinical situation; 4) there was no longer differentiation between node-negative and node-positive disease. We now further discuss the scientific background that was used to come to the current proposal.

HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE BREAST CANCER (LUMINAL CANCERS)

The main new information comes from four trials suggesting that anthracyclines may not always be needed for this breast cancer subset. The ABC trials, a compilation of three different adjuvant trials, compared six cycles of TC (docetaxel + cyclophosphamide) with six cycles of TAC (addition of adriamycin) in 2,125 patients with HER2 negative early breast cancer.[4] The 4-year invasive disease-free survival was statistically inferior for TC (88.2%) versus TAC (90.7%)(p=0.04), but no overall survival (OS) benefit was observed. In subgroup analyses, the benefit of the addition of anthracyclines was mainly derived from the triple negative breast cancer (TNBC) subgroup (HR 1,42; 95% CI 1.04 – 1.94), while TC seemed to perform equally well as TAC for the ER positive cohort with up to three involved nodes. The Hellenic Oncology Research Group compared 6x TC versus 4x dose dense FEC followed by 4x dose dense docetaxel in 650 node-positive BC patients, with mainly ER positive (89%) tumors.[5] The

3-year DFS was numerically higher (91.1%) for TC than for the anthracycline arm (89.5%, p=0.57), while OS was similar. The Danish breast cancer group measured TOP2A amplification in a large set of early breast cancers, excluded from their trial those with TOP2A amplification (16% of the population) because of the presumed benefit of anthracyclines in tumours with TOP2A activation.[6] Patients having tumours without TOP2A activation (n=2,012) were randomised to 6x TC or 3x EC followed by 3x docetaxel. There was no difference in either DFS or OS between both groups in this TOP2A non-amplified group. Finally, the WSG phase III Plan B trial randomised 2,449 patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer, to adjuvant 6x TC or 4x EC → 4x docetaxel. Forty-one percent of these patients were node-positive, 42% had grade 3 tumours and 18% had hormone receptor negative tumors.[7] After a median follow-up of 61 months, similar 5-year DFS of 89.9% [88.1%-91.7%] *vs.* 90.2% [88.4%-92.0%] and 5-year OS of 94.7% [93.4%-96.1%] *vs.* 94.6% [93.2%-96.0%] were observed in the TC and in the anthracycline arms, respectively.

The results from these trials are not completely uniform and conclusive, but we can now state that non-anthracycline regimens such as TC can be an acceptable choice for lower risk luminal disease (N0 or limited number of involved nodes), in patients at high cardiac risk, or those wanting to avoid the very small but clinically significant risk of heart failure (<1%) and secondary leukaemia (+/- 0,5%) associated with anthracyclines.

The optimal number of TC cycles, four (based on the landmark US Oncology Research Trial 9735) or six (based on the four trials discussed above) remains to be defined, but it is unlikely that a randomised trial evaluating four versus six TC cycles will ever happen.[8]

These data do not lead to the conclusion that anthracyclines could/should be omitted for all patients with hormone receptor positive tumours requiring chemotherapy, but provide a valid alternative for lower risk luminal tumours or patients desiring to avoid the cardiac/haematological risk associated with anthracyclines.

TRIPLE NEGATIVE BREAST CANCER (TNBC)

The trials mentioned above, omitting anthracyclines, also included smaller proportions of triple negative breast cancers. However, given the trend for anthracycline benefit in the ABC trials, and the small number of triple negative tumours in the other previously mentioned trials, we suggest using anthracycline-free regimens (four or six TC) only for elderly/less fit patients or patients at high cardiac risk.

The use of carboplatin remains controversial in the whole population of TNBC. As mentioned in the previous 2014 guidelines, the addition of carboplatin consistently leads to a higher pCR rate in TNBC and in particular *BRCA*-mutated tumors.[3,9,10] However, (haematological) toxicity is increased, and outcome data are inconsistent; in GEPARSIXTO, carboplatin increased 3-year DFS substantially in TNBC (85.8% *vs.* 76.1%, p=0.03) while in CALGB 40603, there was no significant benefit on EFS for adding carboplatin (HR 0.84, p=0.36).[11,12] In addition, the TNT trial in metastatic TNBC patients suggests that carboplatin is mainly needed in patients with germline *BRCA* deficiency, and it seems acceptable to add carboplatin in the neoadjuvant setting for germline *BRCA* positive TNBC.[12] Whether carboplatin should be added for patients without a *BRCA* germline mutation remains controversial; in GEPARSIXTO, the addition of carboplatin improved DFS also in patients without a *BRCA* mutation.[13] A subset of patients without germline *BRCA* mutation (those with homologous recombination deficient (HRD) tumours) may also derive benefit from carboplatin, but there is no clear conclusion or recommendation on how HRD is optimally measured, and which subgroups without germline *BRCA* mutation derive benefit from adding carboplatin. This question is therefore still controversial.

The CREATE-X study, a Japanese and South Korean trial in HER2 negative breast cancer, evaluating adjuvant capecitabine in patients with residual tumour after neoadjuvant chemotherapy, showed that six to eight cycles of capecitabine 1,250 mg/m2, twice per day (days 1- 14) every three weeks, improve 5-year DFS (74.1% *vs.* 67.6%, p=0,01) and 5-year OS (89.2% *vs.* 83.6%, p=0,01).[14] In subgroup analyses, the benefit was mainly present for TNBC (32% of the population); hazard ratio for TNBC was 0.58 (0.39-0.87) *vs.* 0.81 (0.55-1.17) for hormone receptor positive breast cancer. Full dose capecitabine was used in this population and resulted in 73% hand foot syndrome. It is important to keep in mind that Caucasian women will likely tolerate capecitabine even less than Japanese women, so it may be prudent to use the more classical 1,000 mg/m2 dose if this (not reimbursed) regimen is considered post-neoadjuvant chemotherapy, but the efficacy of a lower capecitabine dose is not proven in the (neo)-adjuvant setting.

HER2 POSITIVE BREAST CANCER

In the neoadjuvant setting, new data have emerged concerning the addition of pertuzumab to chemotherapy and trastuzumab.[15] Dual blockade with pertuzumab and trastuzumab consistently and significantly increases the pCR rate in HER2+ disease (particularly hormone receptor negative disease), but the neoadjuvant studies failed to show any

KEY MESSAGES FOR CLINICAL PRACTICE

1. In hormone receptor positive early breast cancer, more and more data becomes available on anthracycline-free regimens, such as six times docetaxel plus cyclophosphamide.

2. In triple negative breast cancer, the exact place of platinum added to anthracycline taxane-based chemotherapy remains unclear. In case of incomplete partial response after neoadjuvant chemotherapy, adjuvant capecitabine could be considered.

3. In HER2 positive early breast cancer, there are opposite trends with therapy de-escalation in low risk tumours (e.g. paclitaxel + trastuzumab without anthracycline), while escalation strategies with addition of pertuzumab may be considered in high risk tumours.

DFS or OS benefit by adding pertuzumab or lapatinib, not surprisingly since these studies were not at all powered to demonstrate survival benefits.

A variety of chemotherapy backbone regimens have been used in the neoadjuvant setting. NeoSphere showed that the addition of pertuzumab to docetaxel and trastuzumab significantly increases pCR, but this regimen cannot really be regarded as the most optimal neoadjuvant regimen since the anthracycline part in this study was given after surgery.[16] Tryphaena compared an anthracycline-containing regimen followed by docetaxel, trastuzumab and pertuzumab (starting with FEC, or later with docetaxel), and a third arm containing the BCIRG-006 TCH regimen with the addition of pertuzumab (TCH-P), leading to high (similar) pCR rates in the three arms.[17,18] In the Kristin study, TCH-P was superior to T-DM1 plus pertuzumab.[19] ISPY2 used twelve weeks of paclitaxel, trastuzumab and pertuzumab followed by four cycles of AC, while the TRAIN2 study used 27 weeks of paclitaxel plus trastuzumab and pertuzumab or 3x FEC followed by eighteen weeks of weekly paclitaxel, both combined with trastuzumab and pertuzumab.[20,21] pCR rates in the pertuzumab arms in these studies range from 45% to 68%, but cross-trial comparisons should not be done, and all studied regimens seem acceptable if a pertuzumab combination is chosen.

Recently, the adjuvant Aphinity trial was presented at the 2017 ASCO Annual Meeting.[22] In this large phase III study, chemotherapy (anthracyclines followed by taxanes + trastuzumab, or TCH) with or without pertuzumab was evaluated in 4,805 patients with HER2 positive early breast cancer. The 3-year invasive DFS, the primary endpoint, was 94.1% in the pertuzumab arm versus 93.2% in the control arm, leading to a HR of 0.81, p=0.045. The rate of grade ≥3 diarrhoea was 9.8% versus 3.7%, respectively. Although the study met its primary endpoint, the clinical significance of a 0.9% iDFS benefit without an OS benefit (data not mature yet) is questionable for the whole population. Two subgroups derived the most benefit of adding pertuzumab to trastuzumab, namely node-positive and hormone receptor negative tumours. For node-positive disease, HR for iDFS was 0.77 (92.0% *vs.* 90.2%, p=0.019) while for hormone receptor negative disease, HR for iDFS was 0.76 (92.8% *vs.* 91.2%, p=0.085). Further follow-up is required to confirm or identify subgroups with more pronounced benefit.

The exact place for neoadjuvant and adjuvant pertuzumab remains questionable. Short courses of pertuzumab combined with neoadjuvant chemotherapy and trastuzumab may be a reasonable approach to improve pCR rates, and this is approved by the FDA and EMA in this setting, but not reimbursed in Belgium. If pertuzumab is used, it may be reasonable to use any of the studied chemotherapy backbones with pertuzumab and trastuzumab. TCH-P is the best studied anthracycline-free regimen in this setting, with potentially less cardiac toxicity. In the adjuvant setting, the use of pertuzumab should probably be restricted to high-risk population (e.g. node-positive and hormone receptor negative disease), but this requires EMA approval and reimbursement by RIZIV/INAMI.

CONCLUSION

Table 1 displays a framework that can be used for selecting chemotherapy regimens in early breast cancer patients, but choosing the most optimal regimen requires careful evaluation of the pros and cons of available chemotherapy regimens for each individual patient and setting as well as discussion with patients.

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