Adjuvant and neoadjuvant chemotherapy regimens in breast cancer: summary from the BSMO breast cancer task force meeting

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Knowledge on adjuvant and neoadjuvant chemotherapy regimens in breast cancer is increasing rapidly. Many different regimens are available: some have been compared with each other, but still many questions remain to be answered. At the breast cancer task force meeting of the Belgian Society of Medical Oncology (BSMO) in Brussels, on February 21st 2014, 41 medical oncologists involved in breast cancer management reviewed the most important recent data. The task force discussed a framework for regimen selection in clinical practice. The authors of this paper summarised the literature and meeting discussion, highlighting controversial areas.

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Adjuvant chemotherapy

Introduction: evolution in adjuvant chemotherapy regimens

Adjuvant chemotherapy improves outcome for women with high-risk breast tumours. The first issue is how to select women for adjuvant (or neoadjuvant) chemotherapy. This topic is beyond the scope of the present manuscript, but several guidelines are available.[1] Breast cancer biological subtype, besides tumour extent, has become an important factor in the decision process. Chemotherapy regimens were initially developed for all breast cancer subtypes, but regimens are becoming more and more subtype dependent. Hundreds of randomised studies have been performed in the past on various chemotherapy regimens. It is very difficult to provide an overview of all studies that have ever been performed; we have not been able to find any review that has attempted to do this in the last decade. We refer to the most recent Oxford overview for details on individual trials from the last two decades.[2] For this manuscript, we decided to select landmark studies that can have a major impact on neo/adjuvant therapy regimen choice.

Figure 1 gives an overview of +/-30 years of adjuvant chemotherapy studies. Cyclophosphamide, methotrexate, and fluorouracil (CMF) was the first adjuvant chemotherapy shown to improve outcome in breast cancer, but was generally replaced by anthracycline-containing regimens that performed better. In the last decade, taxanes have come into play, and several so-called 'third generation' regimens, containing both anthracyclines and taxanes (in combinations or sequentially) are currently the standard of choice in many settings.[3,4] Several

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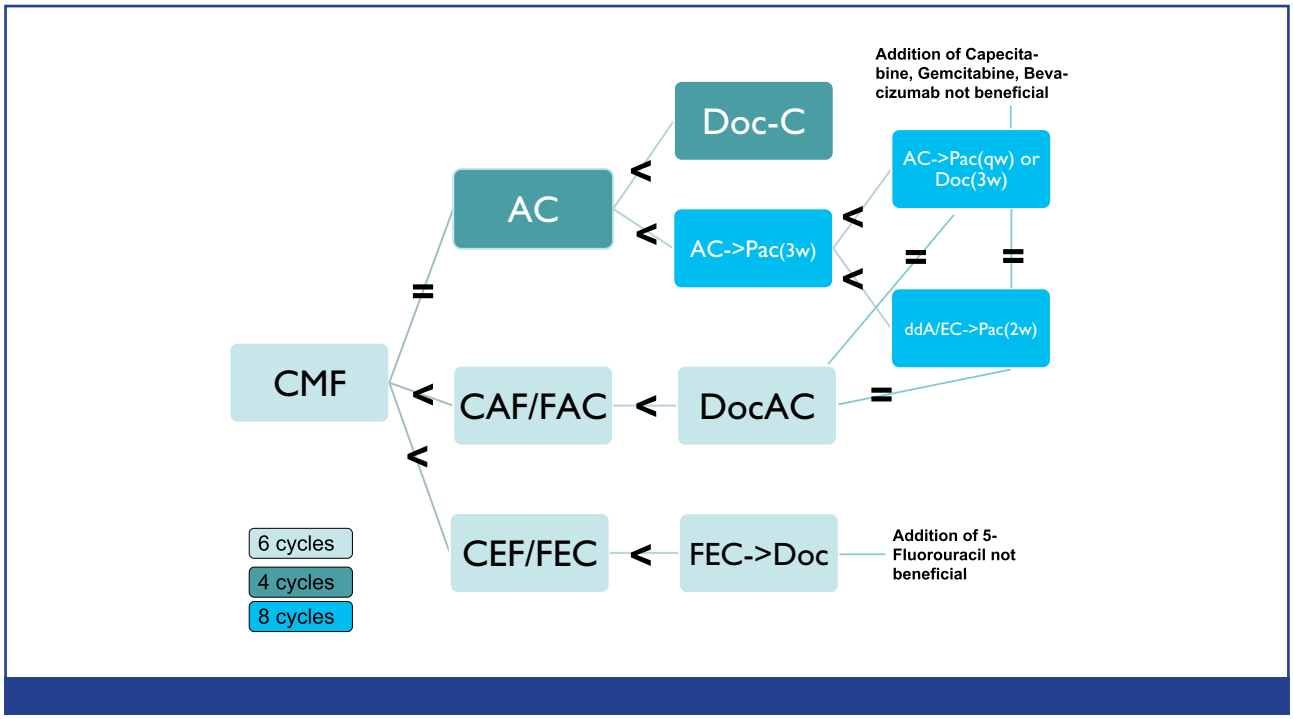

Figure 1. Overview of the most important adjuvant chemotherapy studies in breast cancer. < indicates that the regimen on the right was superior to the regimen on the left for the most relevant endpoints. = indicates that the regimen on the right was equal to the regimen on the left for the most relevant endpoints.

A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = fluorouracil; M = methotrexate; Doc = docetaxel; Pac = paclitaxel; dd = dose dense; qw = weekly; w = weeks interval.

variants of the latter exist, and some but not all have been compared with each other.

Dose dense chemotherapy

An important recent evolution has been to use dose dense chemotherapy (giving same agents and total dose as conventional chemotherapy but with shorter intervals, in most cases every two weeks instead of every three weeks with the help of granulocyte colony stimulating factor, G-CSF). In contrast to 'high dose chemotherapy' (giving higher cumulative and/or per cycle dose), recent dose dense studies show overall improved outcome compared to non dose dense regimens. A 2012 review/meta-analysis (not including the recent large study from Cognetti) showed that dose dense chemotherapy improves disease-free survival (DFS) with a HR of 0.83 (95% CI 0.73-0.95, p 0.005) independent of hormone receptor status, but not overall survival (OS) (p 0.06).[5,6] Other meta-analyses have been done, but many of the involved studies used both a more dose dense and dose intense chemotherapy (higher cumulative dose in the experimental arm), where it is difficult to assess the true impact of dose densification alone.[7] *Table 1* shows four important 'true' dose dense studies that have been presented so far, where exactly the same dose and number of cycles was given in both arms, the only difference being shorter intervals between cycles (two weeks instead of three weeks). The studies from Venturini and Cameron were 'negative' but could be criticised for using very low dose anthracycline (Venturini), only densification of part of the regimen (Cameron), no use of taxane (both), and including a large proportion of node negative patients (both).[8,9] In contrast, the studies by Citron and Cognetti integrate a taxane, are only investigated in node positive patients, and both showed clear improvement in outcome without significant impact on toxicity.[6,10] Dose dense chemotherapy was associated with a slight increase in anaemia and mucositis, but less neutropenia, and although this is a perpetual concern, there was no impact on cardiac events, leukaemia or myelodysplasia with the current follow-up periods reported in these studies.[5]

Optimal taxane regimen

In the dose dense trials from Citron and Cognetti, one could criticise that the taxane part of the two studies was suboptimal: paclitaxel every three weeks (q3w) has been shown to be inferior compared to weekly paclitaxel and

Table 1. 'Pure' adjuvant dose dense studies in early breast cancer.

Author (n)	N status	Control arm	Dose dense (+CSF)	Outcome
Citron (n=1992)	100% N+	4xAC(3w)->4xPac(3w)	4xAC(2w)->4xPac(2w)	DFS ↗ OS ↗*
Venturini (n=1214)	66% N0	6xFE60C(3w)	6xFE60C(2w)	DFS = OS =
Cameron (n=4391)	47%N0	4xE100(3w)->4xCMF/X	4xE100(2w)->4xCMF/X	DFS = OS =
Cognetti (n=2091)	100% N+	4x(F)E90C(3w)->4xPac(3w)	4x(F)E90C(2w)->4xPac(2w)	DFS ↗ OS ↗* 5-FU no benefit

N0 = no lymph node involvement; N+ = lymph node involvement; DFS = disease free survival; OS = overall survival; 5-FU = 5-fluorouracil; X = capecitabine; other abbreviations, see Figure 1.
** Benefit in hormone sensitive and hormone insensitive tumours.*

3-weekly docetaxel in metastatic breast cancer, and is not used anymore in breast cancer.[10] A large four arm adjuvant study evaluated optimal use of taxanes in early breast cancer.[11] In a 2x2 factorial design, 4,950 patients were randomised to paclitaxel or docetaxel, and to weekly or 3-weekly administration. The 3-weekly paclitaxel regimen was clearly inferior in terms of DFS compared to weekly paclitaxel and 3-weekly docetaxel. The only arm that showed a significant benefit in OS is the weekly paclitaxel arm. Paclitaxel weekly and docetaxel 3-weekly performed more or less similar for outcome, but 3-weekly docetaxel was associated with significantly higher grade III or higher toxicity compared to weekly paclitaxel, for instance febrile neutropenia 16% versus 1%, stomatitis 5% versus 0%, fatigue 9% versus 3%, while neuropathy was higher for weekly paclitaxel than 3-weekly docetaxel (8% versus 4%).
Six cycles of dose dense paclitaxel (175 mg/m^2 q2w), given after an anthracycline regimen, have been compared to weekly paclitaxel in terms of efficacy in the SWOG 0221 study and no difference in DFS was reported.[12] However, grade III or higher toxicity was clearly higher for the dose dense administration versus weekly administration of paclitaxel: musculoskeletal problems 11% versus 3%, allergy 14% versus 6%, neurological problems 17% versus 10%. This study suggests that paclitaxel weekly is a better option than dose dense paclitaxel (q2w).

Optimisation of anthracycline taxane combinations
The concomitant administration of anthracyclines within the TAC regimen (docetaxel, doxorubicin, and cyclophosphamide) has been evaluated in several settings. In the NSABP B-38 there was no difference in DFS and OS between six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) with four cycles of dose-dense (dd) doxorubicin and cyclophosphamide (AC) followed by four cycles of dd paclitaxel while the toxicity profile was different, for instance grade three to four toxicities for TAC and dose dense chemotherapy were 9% versus 3% for febrile neutropenia, <1% versus 7% for sensory neuropathy, and 7% versus 2% for diarrhoea.[13] BCIRG 005 showed no difference in outcome between six cycles of TAC and four cycles of AC followed by four cycles of docetaxel every three weeks (q3w).[14] Also here, TAC was associated with more febrile neutropenia and thrombocytopenia, while with the sequential regimen, more neuropathy, nail changes and myalgia were reported. On the contrary, NSABP-30 showed that four cycles of TAC was associated with worse DFS compared to four cycles of AC followed by four cycles of docetaxel every three weeks.[15] Before G-CSF was administered routinely with the TAC regimen, febrile neutropenia (with occasional toxic deaths) was a major limitation for that regimen, but with G-CSF and/or antibiotics prophylaxis, the febrile neutropenia rate seems clinically acceptable.

NSABP-38 compared TAC versus dd AC and paclitaxel as previously described, but also the addition of gemcitabine added to paclitaxel.[15] Gemcitabine did not improve outcome while it increased toxicity. The addition of capecitabine to anthracycline and taxanes was also evaluated, but results were inconclusive.[16] Bevacizumab addition did not improve overall survival in triple negative breast cancer.[17] The previously mentioned study by Cognetti

Table 2. Chemotherapy regimens used in pivotal studies for HER2 positive breast cancer.

Trastuzumab (T) use	Study	Control arm	Trastuzumab arm
Concurrent	BCIRG 006	4xAC->4xDoc	4xAC->4xDoc+T 6xDocCarboT (TCH)
	NSABP B-31	4xAC->4xPac(3w) or 12xPac(qw)	4xAC->4xPac(3w) or 12xPac(qw) +T
Sequential	HERA	Chemo	Chemo->T1y Chemo->T2y
	PACS-04	6xFEC or 6xEDoc	6xFEC or 6xEDoc ->T1y
Concurrent versus sequential	NCCTG N9831	4xAC->12xPac(qw)	4xAC->12xPac(qw)+T1y 4xAC->12xPac(qw)->T1y

T = trastuzumab; y = years; Carbo = carboplatin; other abbreviations, see Figure 1.

had a 2x2 factorial design, not only looking at the value of dose densification, but also evaluating the added value of 5-fluorouracil (5-FU).[6] The hazard ratio for adding 5-FU was 1.0 indicating that 5-FU is not required in anthracycline taxane adjuvant regimens as administered in this study.

The study by Jones questioned the replacement of doxorubicin by docetaxel, and compared four cycles of AC with four cycles of 'TC' (docetaxel plus cyclophosphamide).[18] The latter was clearly superior in terms of DFS and OS, and the results raise the question whether we need anthracyclines anyhow in HER2 negative breast cancer. A small neoadjuvant Chinese study suggested that outcome was better for six cycles of 'TAC' versus 'TC'.[19] Larger studies are currently ongoing to investigate this question.

Chemotherapy regimens in HER2 positive disease

Table 2 shows the chemotherapy regimens that have been used in the pivotal trials with trastuzumab in HER2 positive disease.[20] Many different chemotherapy regimens, mostly variants of an anthracycline and taxane regimen, have been used, but comparative studies between the different chemotherapy regimens are generally lacking. Dose dense chemotherapy has been poorly investigated in this setting. BCIRG006 also evaluated a non-anthracycline regimen, 'TCH' (docetaxel + carboplatin + trastuzumab).[21] As expected, TCH and AC-TH (doxorubicin + cyclophosphamide – docetaxel trastuzumab) performed significantly better than AC-T (doxorubicin + cyclophosphamide – docetaxel). The study was not powered to compare TCH and AC-TH. DFS was 3% lower at 65 months for TCH compared to AC-TH, but this difference was not statistically significant, and TCH was associated with significantly less cardiac failure and secondary leukaemia than the anthracycline arms. There is currently a heavy scientific discussion ongoing on whether anthracyclines are still necessary in (neo-) adjuvant chemotherapy regimens for HER2 positive breast cancer. A single arm study with twelve weeks of paclitaxel and one year of trastuzumab in HER2+ breast tumours ≤3 cm without lymph node involvement showed DFS of 98,7% after median follow-up of 3.6 years, fuelling this discussion further.[22]

Neoadjuvant chemotherapy

HER2 negative disease

The number of randomised trials evaluating neoadjuvant chemotherapy regimens is extremely small compared to the number of adjuvant chemotherapy trials.[23] Most neoadjuvant regimens are selected on the basis of adjuvant chemotherapy studies, and extrapolated to the neoadjuvant setting. *Table 3* shows the most relevant randomised neoadjuvant trials integrating taxanes. The largest trial, NSABP-B27, and also a meta-analysis including seven trials, showed improved pathological complete response rate (pCR) with the addition of taxane, but surprisingly showed no improvement in DFS and OS, in contrast to the many adjuvant studies. Patients achieving a pCR had a significantly better DFS and OS regardless of the regimen they received. Nevertheless, it is generally accepted that a taxane should be part of a neoadjuvant chemotherapy regimen, based on the adjuvant data.

As triple negative breast cancer (TNBC) has clinical and molecular similarities to BRCA-1 associated breast cancers, there has been significant interest in using platinum

Table 3. Selection of important neoadjuvant randomised trials incorporating taxanes.

Author (n)	Control arm	Experimental arm	Outcome
NSABP-B27 (n=2411)	4xAC->S	4xAC->S->4xDoc 4xAC->4xDoc->S	pCR ↗ with Doc DFS = OS =
Aberdeen (n=162)	PR/CR after 4xCVAP: 4xCVAP	PR/CR after 4xCVAP: 4xDoc	pCR ↗ DFS ↗ OS ↗
ACCOG (n=363)	6xAC	4xADoc	pCR = DFS = OS =
Dieras (n=200)	4xAC->	4xAPac	pCR ↗ DFS ↗ OS ↗
Meta-analysis (n=2455); 7 trials	Anthracycline based	Anthracycline based + taxane	pCR ↗ with sequential, but not concomitant taxane. DFS =

S = surgery; pCR = pathological complete response rate (in breast and axilla); PR = partial response; CR = complete response; other abbreviations, see Figure 1.

compounds in TNBC, because these agents cause double-strand DNA breaks which cannot be correctly repaired in cells deficient in homologous recombination repair mechanisms. Several studies have already evaluated neoadjuvant platinum-based therapy in patients with TNBC, the most important of which are summarised in *Table 4*.[24-27] A recent meta-analysis by Petrelli et al demonstrates that neoadjuvant chemotherapy containing cisplatin or carboplatin significantly increases the rate of pCR compared with the non-platinum agents (RR=1.45, 95% CI 1.25-1.68; p< 0.0001).[28] When patients with non-triple negative breast cancer were compared to triple negative breast cancer patients, there was a three-fold increase in pCR rate when the triple negative breast cancer patients were treated with platinum-based therapy (RR 3.32, 95% CI 2.39-4.61; p<0.0001).

An important study of this meta-analysis was CALBG 40603, a neoadjuvant randomised phase II study presented at SABCS 2013 by Sikov et al, analysing the impact of the addition of 3-weekly carboplatin (AUC=6) and/or bevacizumab to weekly paclitaxel followed by dose dense doxorubicin and cyclophosphamide on pCR rate in stage II and III TNBC patients.[27] The benefit on the pCR rate in breast/axilla (ypT0/isN0) was significant for the addition of carboplatin (Odds ratio 1.7; p=0.0029) while it was not significant for the addition of bevacizumab (Odds ratio 1.36; p=0.06). The addition of bevacizumab was also associated with higher toxicity. The chemotherapy arm including carboplatin was better tolerated than the chemotherapy arm including both carboplatin and bevacizumab, but was still associated with significant grade III or higher toxicity: 56% neutropenia, 20% thrombocytopenia, 12% febrile neutropenia, and 6% stopped treatment due to toxicity. Therefore the Belgian Breast Cancer Task Force decided to setup a neoadjuvant phase II study to examine the activity of 12-weekly paclitaxel at 80mg/m^2 in combination with 12-weekly carboplatin (AUC=2) followed by four cycles of dose dense epirubicin and cyclophosphamide every two weeks. In ovarian cancer, weekly administration of carboplatin and paclitaxel is as effective as 3-weekly administration of this combination, and associated with less toxicity.[29] The purpose of the BSMO study in triple negative breast cancer is to decrease severe toxicity and/or augment the dose density of the weekly carboplatin and paclitaxel combination potentially resulting in a higher pCR rate. The study is expected to start in the second half of 2014, and all Belgian sites are welcome to participate.

HER2 positive disease

Several studies have consistently shown that addition of trastuzumab to chemotherapy improves pCR rate, and the NOAH trial also showed improved survival.[30,31]

Table 4. Selection of most relevant neoadjuvant randomised trials incorporating carboplatin.

Author (n)	Control arm	Experimental arm	Outcome
Sikov (n=433) ***All TN***	12xPac(qw) -> 4xddAC (+/- Bev)	12xPac(qw)+4xCarbo(AUC6)-> 4xddAC (+/- Bev)	pCR 49 -> 60%*
Geparsixto (n=595) ***53% TN***	18x NPLD20mg/m^2 + Pac(qw)	18x NPLD20mg/m^2 + Pac(qw)+Carbo(AUC1,5)	pCR 37 ->47%* (TN 38 -> 59%*)
Alba (n=94) ***All TN***	4xEC -> 4x Doc100	4xEC -> 4x Doc75 + Carbo(AUC6)	pCR 35 -> 30%

*Bev = Bevacizumab; TN = triple negative; NPLD = non-pegylated liposomal doxorubicin; AUC = area under the curve; * indicates significant difference.*

This has led to the standard use of anthracyclines, taxanes and trastuzumab in this setting, just like in the adjuvant setting. However the optimal regimen remains to be defined. In a recent study, women with operable HER2 positive invasive breast cancer were randomly assigned to sequential treatment with fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC-75) q3w for four cycles followed by twelve cycles of paclitaxel weekly and trastuzumab, while those randomly assigned to the concurrent treatment group received paclitaxel and trastuzumab followed by FEC-75 q3w and trastuzumab.[32] pCR rate and cardiac toxicity were similar for the sequential and concurrent treatment groups, so the classical sequence of an anthracycline followed by taxane and trastuzumab can still be considered the current standard. The integration of new targeted agents like pertuzumab, lapatinib and T-DM1 is very promising, but the optimal way to integrate them is still uncertain, and they are not available in Belgium in this setting at present.

How to select regimens for individual patients?

It is a challenge to select an optimal chemotherapy regimen for an individual patient that we see in daily clinical practice. Many regimens can be identified, and the choice of a specific regimen not only relies on efficacy data, but also on specific toxicities, costs, and reimbursement and availability of drugs and growth factors. Also patient preference can play a role, for instance the number of chemotherapy administrations, or undesired side effects (e.g. neuropathy) for individual patients.

Table 5. Framework for selection of ADJUVANT chemotherapy regimens in function of tumour type and lymph node involvement.

	HER2 neg ER pos	Triple neg	HER2 pos
N+	4xAC/EC*dd° -> 12xPac qw 4xAC/EC* ->12xPac qw 4xAC/EC*dd° -> 4xPac175dd° 3xFEC->3xDoc (6xDocAC + G-CSF) (4 (to 6) x DocC)	4xAC/EC*dd° -> 12xPac qw 4xAC/EC*dd° -> 4xPac175dd° (12xPac+4xCarbo -> 4xEC*dd°)** (3xFEC->3xDoc) (6xDocAC + G-CSF) (4 (to 6) x DocC)	4xAC/EC* ->12xPac+Trast 3xFEC -> 3xDoc+Trast 6xTCH (4xDocC+Trast) (12xPac+Trast)°°
N-	4xAC/EC* -> 12xPac qw 3xFEC->3xDoc 4xDocC	4xAC/EC*dd° -> 12xPac qw 4xAC/EC*dd° -> 4xPac175dd° 4xAC/EC* -> 12xPac qw (12xPac+4xCarbo -> 4xEC*dd°)** 3xFEC->3xDoc (6xDocAC + G-CSF) (4 (to 6) x DocC)	4xAC/EC* ->12xPac+Trast 3xFEC -> 3xDoc+Trast 6xTCH (4xDocC+Trast) (12xPac+Trast)°

*G-CSF = granulocyte colony stimulating factor; qw = weekly; neg = negative; pos = positive; Trast = trastuzumab; TCH = Docetaxel-Carboplatin-Trastuzumab. °dd = dose dense = q2w + G-CSF. °°only data from a single arm phase II study in tumours <3cm, N0. *EC = epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2. **only neoadjuvant data: consider if BRCA associated tumour. Other abbreviations, see previous tables.*

Table 6. Framework for selection of NEO-ADJUVANT chemotherapy regimens in function of tumour type and lymph node involvement.

	HER2 neg ER pos	Triple neg	HER2 pos
N+	4xAC/EC*dd° -> 12xPac qw 4xAC/EC* -> 12xPac qw 4xAC/EC*dd° -> 4xPac175dd 3xFEC->3xDoc (6xDocAC + G-CSF) (4 (to 6) x DocC)	12xPac+12xCarbo(AUC2)**->4xEC*dd° 12xPac+4xCarbo(AUC6)->4xEC*dd° 4xAC/EC*dd° -> 12xPac qw 4xAC/EC*dd° -> 4xPac175dd° (3xFEC->3xDoc) (6xDocAC + G-CSF) (4 (to 6) x DocC)	4xAC/EC*->12xPac+Trast 3xFEC -> 3xDoc+Trast 6xTCH (4xDocC+Trast) (12xPac+Trast)°°
N-	4xAC/EC* -> 12xPac qw 3xFEC->3xDoc 4xDocC	12xPac+12xCarbo(AUC2)**->4xEC*dd° 12xPac+4xCarbo(AUC6)->4xEC*dd° 4xAC/EC*dd° ->12xPac qw 4xAC/EC*dd° ->4xPac175dd° 4xAC/EC* ->12xPac qw 3xFEC->3xDoc (6xDocAC + G-CSF) (4 (to 6) x DocC)	4xAC/EC* ->12xPac+Trast 3xFEC -> 3xDoc+Trast 6xTCH (4xDocC+Trast) (12xPac+Trast)°°

*°dd = dose dense = q2w + G-CSF. °°only data from a single arm phase II study in tumours <3cm, N0. *EC = epirubicin 90 mg/m², cyclophosphamide 600 mg/m². **consider Belgian Phase II study in preparation. Other abbreviations, see previous figures.*

As a general rule, one should always try to use regimens that have been evaluated in clinical trials as much as possible. The big question is in how far extrapolations from data in specific populations/studies are allowed. Uncertainty remains on several important issues :

- The paclitaxel regimen used in the dose dense studies was paclitaxel 175 mg/m² q2w, but the data for weekly paclitaxel are at least as promising, and the latter regimen is less toxic. It could be considered to use paclitaxel weekly in regimens where anthracyclines are given dose dense, although this regimen has not been studied independently.
- Dose dense studies have mainly been studied in lymph node positive disease. Can these regimens also be given for instance in node negative TNBC?
- Can we extrapolate chemotherapy regimen studies from the HER2 negative setting to the HER2 positive setting? Dose dense regimens? Omission of 5-FU?
- Do we need to make a distinction between hormone sensitive and hormone insensitive HER2 negative disease? Use of dose dense regimens, 'TC' regimen, etc.?
- In how far can we extrapolate data from adjuvant to neoadjuvant setting and vice versa? The data for addition of carboplatin to neoadjuvant chemotherapy regimens in TNBC are very promising and could be considered as a new standard for TNBC in neoadjuvant setting. But should we use regimens without carboplatin in adjuvant setting for TNBC which would imply that patients receive different regimens in adjuvant and neoadjuvant settings for the same disease?

Conclusion

There is no easy solution for the choice of chemotherapy regimens. The breast cancer task force of the BSMO reviewed the available evidence (after preparatory work by H. Wildiers) in a meeting on 21-02-2014 in Brussels, and discussed a pragmatic framework for selection of adjuvant and neoadjuvant chemotherapy regimens. The summary is shown in *Table 5* and *Table 6*. This framework is not set in stone, and will need adaptation when new data becomes available in the future. The framework provides a choice of various regimens for different settings, depending on breast cancer subtype and lymph node involvement. The order of regimens was established by putting the most preferred choices first, and mentions the less preferred regimens subsequently. But it should be acknowledged that sites may have specific reasons to change the order of presented regimens, and that specific regimens for individual patients can be preferred for patient related reasons (e.g. fear for toxicity such as cardiac failure or neuropathy, refusal to have sixteen chemotherapy administrations, etc.). The current manuscript is a summary of the

Key messages for clinical practice

1. Many adjuvant and neoadjuvant chemotherapy regimens have been studied in breast cancer care.
2. The choice of a specific regimen not only relies on efficacy data, but also on specific toxicities, patient preference, costs, and availability of drugs.
3. One should always try to use regimens that have been evaluated in clinical trials for each specific setting, but in some situations, extrapolation from one to another setting can be a pragmatic acceptable choice.
4. This manuscript establishes a pragmatic framework for selection of adjuvant and neoadjuvant chemotherapy regimens in breast cancer, summarised in *Figure 6* and *Figure 7*.

meeting by the four authors. We did not aim to make a formal consensus publication with 41 oncologists, which would be a major undertaking, but decided to summarise the literature and meeting among the four co-authors.

A major point of discussion is the use of the 'French' FEC followed by docetaxel regimen (currently often used in Belgium) versus anthracycline regimen without 5-FU and weekly paclitaxel. The former regimen is certainly still a valid regimen as indicated in the flow chart. It has advantages like the fact that only six cycles are needed instead of sixteen and less neuropathy is seen compared to weekly paclitaxel. On the other hand, several severe side effects are much more pronounced for docetaxel (e.g. febrile neutropenia, fatigue), the regimen has not been appropriately evaluated for dose densification (shown to be beneficial in several settings as mentioned above), and the recent study by Cognetti (although only presented and not yet published) showed that addition of 5-FU does not give any benefit, while there is a small risk of very severe toxicity with this drug (in case of Dihydropyrimidine Dehydrogenase Deficiency (DPD)).[6] On the basis of these arguments, we decided to put the French regimen lower in the ranking, but the discussion remains open, certainly for settings where dose densification is not used.

It should also be acknowledged that evidence for dose dense regimens is strongest for triple negative node positive breast cancer, while its use is more debatable for triple negative node negative and hormone sensitive HER2 negative node positive breast cancer.

Lastly, although the results with neoadjuvant chemotherapy including carboplatin in triple negative breast cancer are very promising, there is no level I evidence yet, and the large Geparsixto and Sikov trials were randomised phase II trials not powered to demonstrate improved OS benefit.[26,27] It is unlikely however that a phase III trial with this cheap, off patent, drug will ever be performed. We believe that the data, including a meta-analysis of six randomised neoadjuvant trials with platins are sufficiently solid to justify its use as a standard regimen, certainly in node positive disease.[28]

We hope that this framework provides a useful tool for medical oncologists to select appropriate chemotherapy regimens for their individual patients.

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