Research Review
SPEAKER SERIES

Risk prediction of patients with small HER2-positive tumours and clinical implications
Optimising adjuvant chemotherapy for high-risk patients, focusing on dose-dense therapy
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Dr Richard de Boer is a consultant medical oncologist at the Royal Melbourne Hospital and the Royal Women's Hospital in Melbourne, Australia. Dr de Boer earned his medical degree at the University of Melbourne and completed general medical training at the Royal Melbourne Hospital. He completed a clinical research fellowship in breast and lung cancer at the Royal Marsden Hospital in London with Professor Ian Smith.

Dr de Boer's primary areas of clinical interest are in breast and lung cancer. His breast cancer research focuses on biological predictors of response/survival, endocrine therapy, anti-angiogenic therapy, treatment-induced bone loss, and bone metastases. He is actively involved in clinical research, examining new treatment strategies, serving as chair of the Clinical Trials Australia Breast Cancer Trials Group, and as a member of the Australian and New Zealand Breast Cancer Trials Group. He is on the steering committees of international trials such as ZO-FAST and FACE.

Dr de Boer is a member of several professional organisations including the Medical Oncology Group of Australia and the American Society of Clinical Oncology. He has authored or co-authored articles appearing in such journals as the *Journal of Clinical Oncology*, *Annals of Oncology*, *The Breast and British Journal of Cancer*.

This publication is a summary of a recent presentation by Dr Richard de Boer, a medical oncologist at the Royal Melbourne Hospital, Victoria, Australia. He spoke to a panel of medical oncologists, oncology specialists and other health professionals, in Hamilton, Auckland and Wellington in November 2009, regarding risk prediction of patients with small node-negative HER2-positive breast cancers and how to tailor their therapy accordingly. He also discussed the use of adjuvant chemotherapy in high-risk breast cancer patients, focusing on the role of dose-dense therapy in the treatment of early-stage breast cancer.

Biological factors are being increasingly used to tailor treatments for breast cancer, thereby resulting in complicated discussions about regimens with patients as well as better treatment options. The two areas addressed by Dr de Boer in his presentation concern firstly the small "low-risk" HER2-positive cancers – arising out of his concern as to how best to manage patients with this type of tumour; an issue that has become a topic of interest worldwide. The second area concerns adjuvant chemotherapy; Dr de Boer has been using dose-dense therapy since a pivotal paper was published in 2003 for its use in a particular group of breast cancer patients. He explained that while this regimen is perhaps not widely used, he considers it one that deserves consideration for certain patient subgroups.

How to select treatment options?

Dr de Boer notes that for many patients different positions can be taken when deciding on treatment, particularly so in the case of patients with small HER2-positive tumours. Whereas guidelines can play an important role, individual trial results and clinical experience are also important factors. Treatment options in Australia and New Zealand are also impacted upon by cost and availability. Adjuvant treatment is increasingly moving away from the anatomic approach that considers that "big is bad" (as defined by tumour size and lymph node involvement), that results in these patients being recommended chemotherapy, and towards a biological approach that considers factors such as grade, hormone receptor status and HER2 status to being important in determining treatment recommendations. Dr de Boer acknowledges that while lymph node involvement is important, size may be primarily determined by time of detection and give less information about the true biology of the tumour. Treatment decisions are increasingly being influenced by biological factors, reflecting the fact that breast cancer is a heterogeneous disease comprising many different subgroups. Molecular analyses are beginning to map out breast cancer into smaller subgroups and the challenge is to match them to treatments. This is mirrored by the 2005 St. Gallen consensus report, which fundamentally changed how treatment is selected.1 Up until then, risk status (risk of recurrence, low, intermediate and high) dominated selection of treatment, but since 2005, hormone responsiveness has become the initial consideration in stratification for systemic therapy, based on emerging evidence that chemotherapy responsiveness may be related to hormone status.

Pros and cons of treatment options

Breast cancer surveillance and early detection is increasingly revealing small node negative tumours, the majority of which are cured by surgery. However, some of these patients will relapse and some will benefit from adjuvant therapies. It can be difficult to decide on the most appropriate course of adjuvant therapy for these patients, with other prognostic factors being seen as increasingly important, including the grade, the hormone status, the degree of hormone positivity, the HER2 status of the tumour and age of the patient. The St. Gallen guidelines define "low risk" as being HER2-negative; patients with HER2-positive tumours are classified as either intermediate or high risk.[2] In discussions with his colleagues, Dr de Boer emphasises that if a woman has a HER2-positive tumour then, irrespective of other factors, it is worth discussing the pros and cons of anti-HER2 targeted treatment with this patient. He observes that increasingly, patients are requesting such discussions so that they better understand their cancer. He recommends that if any negative biological factors are present, the patient should be made aware of these and of all implications involving treatment.

HER2 amplification undesirable

Much data attest to the fact that HER2 overexpression is a negative biological feature. A 1998 paper investigating survival of node-negative breast cancer patients related to HER2 status found that the risk of dying was significantly increased in those with HER2 amplification.[3] Similarly, in 1997, an evaluation by Press and colleagues into how HER2 gene amplification interacts with other prognostic factors in predicting recurrence-free survival in patients with node-negative breast cancer demonstrated that it does not really matter what other factors are considered – if the patient is HER2-positive, then the relative risk starts to increase, particularly in cases that are hormone-negative as well and especially as the tumour increases in size.[4]

Prognosis of HER2-positive pT1N0 tumours and treatment

A survey of experts in 2006 revealed their thinking as to the role of chemotherapy and trastuzumab in patients with node-negative HER2-positive breast cancer, according to the size of the cancer and hormone receptor (HR) status.[5] The majority (74%–96%) considered that for a patient with a 1–2cm hormone-negative cancer, a reasonable regimen would comprise adjuvant chemotherapy plus trastuzumab. Fewer (66%–67%) advocated this regimen for hormone-positive tumours measuring 1–2cm, while less (15%–29%) would use such treatment in tumours of <1cm, but clearly, this treatment approach was felt worthwhile to consider.

The Finnish Breast Cancer Group examined long-term follow-up data (median 9.5 years) in patients diagnosed with pT1N0M0 breast cancer (≤2cm) in Finland between 1991 to 1992.[6] Very few of these patients (5%) had systemic adjuvant therapy. Estrogen receptor (ER), progesterone receptor (PR), erbB2, p53, and Ki-67 expression was determined from tumour tissue microarrays using immunohistochemistry, and the erbB2 (HER2) amplification status was determined using chromogenic in situ hybridisation (CISH). Results showed that 9-year distant disease-free survival (DFS) was significantly worse for those patients with small tumours that were HER2-positive, compared with those with HER2-negative tumours. Women with small tumours of HER2-negative status did remarkably well with no treatment, whereas relapse risks were significantly increased in HER2-positive patients.

How risky is this disease?

At the 2006 San Antonio Breast Cancer Symposium (SABCS), Black and colleagues from the US presented data from T1–2 patients that were node-negative and HER2-positive; a group that at the time did not meet criteria for adjuvant trastuzumab.[7] Of 164 patients, 48% were grade 3, 76% were HR-positive and among patients with tumours of <1cm, 34% had received chemotherapy, 54% endocrine therapy (trastuzumab was not administered). The results showed a moderate risk of recurrence among those with T1a-b or T1c tumours, with a 5-year DFS rate of around 90% in each group, although the event rate was as high as 20%. Dr de Boer predicts that, in view of the small tumour size and node-negative status, most of these patients would have been advised to expect better outcomes. Could outcomes have been improved with other therapies? Further studies are required to assess the relative contributions of chemotherapy/endocrine therapy regimens and of anti-HER2 therapy in reducing recurrence. A similar analysis was performed by a group from Canada, which evaluated 6–7 years of a cancer registry and identified 1245 patients with pT1N0 tumours, 117 (9.4%) of whom were HER2-positive – a figure that Dr de Boer notes is also reported by other studies (not the 20%–25% that is commonly stated in the literature, which relates to larger, node-positive tumours).[8] Dr de Boer highlighted two key results [see figure 1]: 1. Very few of the HER2 tumours were lobular (0.9% and very few were grade 1 (1.7%). In this population, only 17.9% of the HER2-positive tumours were <10mm. Most were larger, of higher grade and were hormone negative – a population that one can consider a recommendation for treatment consisting of trastuzumab and chemotherapy to be quite reasonable. He noted that the more difficult decisions on how to treat come with tumours that are smaller, grade II and hormone receptor (HR)-positive.

	T1pN0 n = 1245	
	HER-2 positive n = 117	HER-2 negative n = 1128
Age at Diagnosis		
Median (range)	56 (29 – 85)	62 (23 – 89)
<30	1 (0.9)	7 (0.6)
30 - 39	11 (9.4)	44 (3.9)
40 - 49	27 (23.1)	201 (17.8)
50 - 59	25 (21.4)	243 (21.5)
60 - 69	30 (25.6)	332 (29.4)
70 - 79	22 (18.8)	259 (23.0)
80+	1 (0.9)	42 (3.7)
Histology		
Ductal	113 (96.6)	1031 (91.4)
Lobular	1 (0.9)	70 (6.2)
Other	3 (2.6)	27 (2.4)
Tumour Grade		
1	2 (1.7)	114 (10.1)
2	40 (34.2)	543 (48.1)
3	72 (61.5)	431 (38.2)
Unknown	3 (2.6)	40 (3.5)
Tumour Size		
Median (range) - cm	1.5 (0.1 – 2.0)	1.5 (0.1 – 2.0)
0.1 – 1.0 cm	21 (17.9)	305 (27.0)
1.1 – 2.0 cm	96 (82.1)	823 (73.0)
2.1 – 5.0 cm	n/a	n/a
> 5.0 cm	n/a	n/a
Unknown	n/a	n/a
ER Status (SP1)		
Negative	77 (65.8)	251 (22.3)
Positive	40 (34.2)	877 (77.7)
LVI Status		
Negative	86 (73.5)	859 (76.2)
Positive	29 (24.8)	235 (20.8)
Unknown	2 (1.7)	34 (3.0)

Most common: 1.1-2.0cm, Grade III IDC, ER-ve

Figure 1. Patient, tumour and treatment characteristics for the T1pN0 cohort by HER2 status

	No. of cases	10yr-RFS	10yr BCSS
ER+ve, HER2-ve	877	79%	91%
ER+ve, HER2+ve	40	77%	90%
ER-ve, Her2-ve	251	78%	86%
ER-ve, HER2+ve	77	68%	76%

- Her2 +ve pts have worse outcomes, especially if also ER-ve
- The high chance of systemic recurrence through 10 yrs is probably sufficient for many clinicians to offer adjuvant trastuzumab, esp if T>1cm
- The actual impact of trastuzumab on risk of relapse is unknown

Figure 2. 10-year breast cancer specific survival (BCSS) and relapse free survival for HER-2 positive pT1N0 tumours[8]

Indeed, the 10-year follow-up data from this research revealed that up to a third of the patients were relapsing [see Figure 2]. For these small, node-negative tumours, Dr de Boer considers these relapse rates to be unacceptably high. Interestingly, in those patients that were hormone-positive and HER2-positive, the results were not dissimilar to HER2-negative tumours. Some clinicians question whether endocrine therapy alone will successfully treat a HER2-positive/HR-positive cancer. Dr de Boer acknowledges that this is a debatable area – some evidence suggests that these tumours are not as responsive to endocrine therapy. However, in this study, those patients that were positive for both seemed to be doing quite well.

High recurrence rates in HER2-positive T1a-bN0 tumours

The results from Norris et al differ from those presented by Rakkhit and colleagues from the MD Anderson group in December 2008 at the SABCS.[9] They reviewed data from 965 T1a-bN0 breast cancers; patients who had received adjuvant chemotherapy or trastuzumab at any time were excluded. As with the Canadian group, around 10% (98 patients) were HER2-positive, reinforcing that this is a small but not a rare group. In addition, 77% were HR-positive and 13% were triple receptor-negative. Of those with HER2-positive tumours, the 5-year, recurrence-free survival (RFS) was 77.1%, compared with 93.7% in HER2-negative patients and 85.2% for triple receptor-negative tumours. Five-year distant RFS was 86.4% in those with HER2-positive tumours versus 97.2% for HER2-negative tumours. Patients with HER2-positive tumours had 2.68 times higher risk of recurrence and 5.3 times higher risk of distant recurrence than those with HER2-negative tumours. In addition, women with HER2-positive tumours had 5.09 times the risk of recurrence and 7.81 times the risk of distant recurrence than women with HR-positive tumours.

These results were replicated in additional data sets from European institutions. Rakkhit and colleagues felt strongly that systemic treatment with HER2-targeted therapies should be considered in this population and that ongoing clinical trials should include such patients.

A summary of the data from these 4 papers show unacceptably high relapse figures – Dr de Boer says we need to be thinking about this when we see these patients, discussing with them all possible treatment strategies.

Treatment of N0 infra-centimetric HER2-positive tumours

French investigators retrospectively analysed data from 127 patients with T1a-b HER2-positive cancers diagnosed since 2005.[10] A total of 20% of tumours were <6mm, 55% were HR-negative, 22% node-positive and 1% lobular. In a cohort of 96 patients (78%) who were node-negative, 37 had chemotherapy plus trastuzumab and 3 had trastuzumab without chemotherapy. Those receiving trastuzumab were mainly of higher risk: grade 2/3 and HR-negative. So far, there have been no recurrences in this group, whereas the 56 patients who did not receive trastuzumab (as they were considered to be better prognosis patients), have had 5 recurrences and 1 death. The researchers recommend including patients with T1a-bN0 HER2-positive tumours in HER-2-targeted adjuvant trials.

Randomised clinical data regarding choice of therapy

The most recent NCCN Guidelines V (2009) consider trastuzumab suitable in almost any tumour and *recommend* if the tumour is greater than 1 cm or there is an involved lymph node: Dr de Boer indicated that his own practice is similar. Four large randomised controlled trials have reported outcomes for adjuvant trastuzumab in HER2-positive tumours: the Breast InterGroup HERA trial (1 or 2 years of trastuzumab given every 3 weeks compared with observation); the NSABPB-31 trial (comparing AC-T with AC-T plus 1 year of trastuzumab); the NCCTG N9831 trial (1 year of adjuvant trastuzumab given either concurrently with, or following, paclitaxel therapy compared with chemotherapy alone), and the BCIRG 006 trial (1 year of adjuvant trastuzumab given with chemotherapy compared with chemotherapy alone). Regarding numbers of 'lower risk' patients (i.e. those with lymph node-negative tumours) – HERA and BCIRG 006 each had about a third, NCCTG N9831 had only 11%, and there were none in the NSABP B-31 trial. A joint analysis of the American studies shows a consistent 10% benefit across all major subgroups in 4-year DFS from adding trastuzumab to the treatment regimen.11 Dr de Boer observed that this begs the question as to whether this result might well translate to all biological subgroups under consideration including those patients with small lymph node tumours.

An analysis of data from node-negative patients in the BCIRG 006 study mirrored the overall results.[12] The two trastuzumab-containing arms were similar and were superior to the non-trastuzumab arm in lymph node-negative patients. In the DFS subpopulations, all subgroups appeared to derive benefit from the addition of trastuzumab.

Likewise, in an analysis of outcomes for subgroups (i.e. pathological tumour size, hormone receptor status, histological grade, nodal status) from the HERA study, all groups appeared to benefit from the addition of trastuzumab.[13]

Importantly, the result appears to be independent of estrogen receptor status. These results were further substantiated in a 2008 analysis by Untch and colleagues, which found that no matter what the subgroup, 3-year DFS was significantly better for trastuzumab-treated patients compared with those not given trastuzumab.[14]

In Australia, under PBS guidelines, adjuvant trastuzumab must be commenced concurrently with chemotherapy, with common regimens being those tested in the large adjuvant studies including AC-TH and TCH. An issue with these regimens is the number of cycles of chemotherapy (6–8) and associated risk of cardiac toxicity, or the potential docetaxel-related toxicity. Dr de Boer therefore looked at other regimens, which may have less randomised evidence, but that may be suitable for patients with T1N0 HER2- positive tumours. Regimens discussed included the FEC-Taxane regimen, and the Taxotere-Cyclophosphamide regimen. Dr de Boer considers that smaller HER2-positive cancers can be treated with the TCyclo regimen (4 cycles) as examined by the Stephen Jones USOG 9735;[15,16] the chemotherapy duration is as short as possible, enables trastuzumab to be started with cycle 1, and has no cardiac toxicity of its own. However, clearly more clinical trial data are needed for this regimen.

In summary, Dr de Boer considers that HER2 overexpression represents a 'bad biology'. It needs to be recognised from the beginning and its importance should be discussed with patients. Much retrospective data are now appearing suggesting that the risk of relapse with small node-negative HER2-positive tumours is higher than one might expect, and that we need to consider how to reduce this risk. There is a question as to whether endocrine therapy is as effective in HER2-positive cancers. In Australia, trastuzumab must be given in combination with a chemotherapy regimen which is where the randomised evidence is; and a regimen such as TC seems to Dr de Boer to be a reasonable option.

Dr de Boer acknowledges that a number of patients will not even need treatment and that trastuzumab will not be of particular benefit for some. Disadvantages of trastuzumab therapy include its expense, potential cardiac toxicity and the year-long duration. More data would be helpful as to the use of trastuzumab and in particular knowing more about markers of pathway activation, which could aid in decision-making as to who is best suited for trastuzumab therapy. The final analysis regarding which patients should receive trastuzumab should weigh up many factors such as recurrence risk, the assumed benefit from standard therapies, including endocrine therapy alone or chemotherapy, and what benefit is expected from trastuzumab for any particular subgroup. Cardiac toxicity is also an issue for consideration. Important factors for cardiac toxicity include age, previous history, baseline ejection fraction, and hypertension. Dr de Boer looks for reasons *not* to give trastuzumab, rather than for reasons *to* give it. Dr de Boer acknowledges that a reasonable and commonly taken stance in small HER2 tumours that are also endocrine sensitive, is a preference for endocrine therapy without trastuzumab, unless another negative factor exists such as high grade or young age. Dr de Boer considers this to be an ongoing debatable area, yet the idea of trastuzumab therapy is starting to expand from just the bigger node-positive cancers to smaller cancers, as indicated by the latest guidelines

Optimising adjuvant chemotherapy for high risk patients: A role for dose-dense therapy in ESBC?

Many questions surround the issue of early-stage breast cancer and choice of chemotherapy for high risk patients. Which regimen is best? Can we avoid anthracyclines? Do we need to avoid them? Do we need a taxane? If yes, which one? If yes, concurrent or sequential? How does dose-dense fit in? What is the best HER2 regimen? How much trastuzumab is needed? Which node-negative patients can be considered high risk? How do we integrate biologicals such as bevacizumab? And critically, how do we pay?

Defining `risk'

The 2006 St. Gallen consensus on risk profiling classifies early breast cancer as low, intermediate and high risk [see Figure 3].[2] The choice of chemotherapy, endocrine therapy and trastuzumab therapy depends on endocrine responsiveness and risk category; clinicians are able to exercise much discretion as to best regimen. According to the St. Gallen risk staging, low risk breast cancer is relatively rare; multiple good prognostic factors are needed to fit this category. The majority of patients are classified as intermediate risk.

The adjuvant treatment paradigm

There are a wide variety of commonly used regimens in the adjuvant setting, from the anthracycline-based therapies dating from 10 to 15 years ago through to the standard North American regimens comprising sequential AC and taxane, to dose-dense therapy and the non-anthracycline regimens, either with or without trastuzumab [see Figure 4].

Increasingly better chemotherapy options have improved the management of patients, as for instance in node-positive breast cancer, where 5-year progression rates have improved from close to 80% with no therapy to the latest generation of therapy (TAC) yielding rates of approximately 25% [see Figure 5].[17-20]

Evolution of chemotherapy regimens in ESBC

NSABP trials established that the outcome from CMFx6 and ACx4 was almost identical and in the ECOG 2197 study, the ATx4 regimen was not significantly different from ACx4. In the 1990s, in a number of trials in Europe and Canada, the CMFx6 regimen evolved into CEF/FECx6 or CAF/FACx6. The classic ACx4-Pacx4 regimen that changed US-based practice was established by the CALGB 9344 trial, which demonstrated that the addition of paclitaxel to the ACx4 regimen reduced the risk of recurrence and death.[21]

The next generation of trials has led to many of our current regimens. In France, the PACS 01 trial compared FECx6 with FECx3+Taxoterex3; the addition of Taxotere significantly improved disease-free and overall survival (OS) and had a favourable safety profile. Similarly, the BCIRG 001 trial established that TACx6 was superior to FACx6 for DFS and OS.

The backbone ACx4-Pacx4 regimen has been extended and compared in two large studies; in ECOG 1199, outcomes supported the use of weekly paclitaxel as a superior strategy in the adjuvant setting over 3-weekly paclitaxel and 3-weekly docetaxel over weekly docetaxel, while the CALGB 9741 study demonstrated improvements in DFS and OS by a dose dense approach whereby chemotherapy was given every 2 weeks with growth factor support.[22]

The most recent clinical trial evidence includes the NSABP B-30, demonstrating that AC-T was superior to TACx4 and ATx4. The BCIRG 005 study showed that TACx6 was equivalent but less toxic than ACx4-docetaxel, and the USON 9735 study showed that TCx4 was superior to standard ACx4.

This variety of regimens offers clinicians choices to tailor therapy to individual patients.

Risk category	Endocrine responsive[a]	Endocrine response uncertain[a]	Endocrine non-responsive[a]
Low risk[b]	ET	ET	Controversial
Node negative AND all of the following:	Nil[c]	Nil[c]	See text
pT[d] ≤2 cm, AND			
Grade 1[e], AND			
No peritumoral vascular invasion[c], AND			
HER2/*neu* gene not overexpressed nor amplified[f], AND			
Age ≥35 years			
Intermediate risk	ET alone, or		
Node negative AND at least one of the following:	CT → ET	CT → ET	CT
pT[d] >2 cm, OR	(CT + ET)[f]	(CT + ET)[f]	
Grade 2–3[e], OR	Trastuzumab[g]	Trastuzumab[g]	Trastuzumab[g]
Presence of peritumoral vascular invasion[c], OR			
HER2/*neu* gene overexpressed or amplified[f], OR			
Age <35 years			
Node positive (1–3 involved nodes) AND			
HER2/*neu* gene not overexpressed nor amplified[f]			
High risk	CT → ET	CT → ET	CT
Node positive (1–3 involved nodes) AND	(CT + ET)[f]	(CT + ET)[f]	
HER2/*neu* gene overexpressed or amplified[f]	Trastuzumab[g]	Trastuzumab[g]	Trastuzumab[g]
Node positive (4 or more involved nodes)			

Figure 3. How is 'risk' defined?

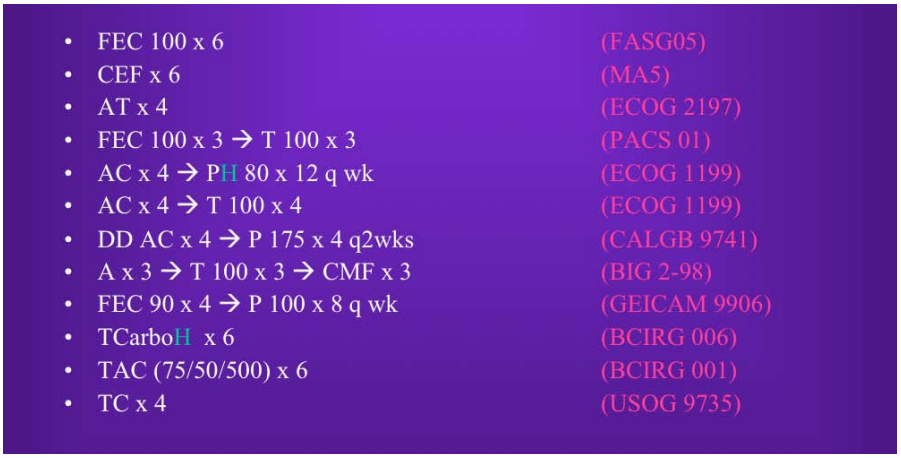

Figure 4. Adjuvant chemotherapy regimens 2009

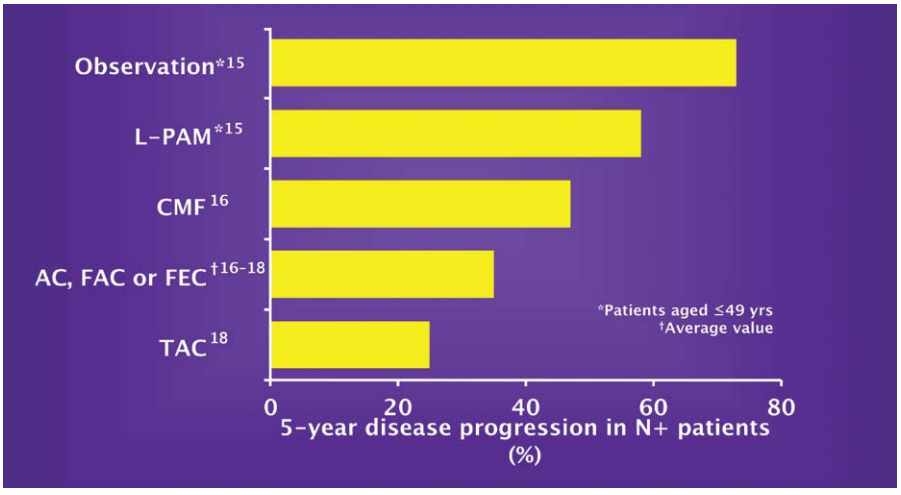

Figure 5. Better chemotherapy options for high-risk EBC patients

Use taxanes sequentially or in combination?

The NSABP B-30 study compared ACx4-Tx4 with ATx4 and with TACx4. Dr de Boer points out the unevenness of this comparison; the longer treatment length offered by the 8 cycles would be expected to be better for these higher risk patients, as indeed it was (yielding a significant advantage in DFS versus the other regimens).[2] The outcomes from the BCIRG programme are more relevant to Dr de Boer's practice. In particular, the 005 study compared TACx6 with AC-Tx4 in HER2 normal, node-positive breast cancer.[24] Despite AC-T delivering a higher dose-intensity for each agent and giving 8 cycles, the DFS and OS results were essentially equivalent, regardless of number of positive nodes, hormone receptor status, and triple-negative receptor status. Notably, sequential therapy led to higher rates of neuropathy, nail changes and myalgia. Dr de Boer noted the lower docetaxel dose in the TAC regimen (75 mg/m^2) than in the sequential schema (100 mg/m^2) and in view of the resulting toxicity profiles, considers TAC to be preferable to AC-T. In Australia, the Pharmaceutical Benefits Advisory Committee allows for prophylactic administration of pegfilgrastim in TAC schedules (not the case in other adjuvant breast cancer treatment regimens), which effectively lowers the febrile neutropenia rate from approximately 40% to a more acceptable 5%.

Where does dose-dense therapy fit?

The concept of dose-dense therapy attempts to improve the effectiveness of chemotherapy by giving the same dose at a shorter treatment interval, thereby decreasing time for tumour regrowth, and hopefully resulting in greater overall cell kill. Over the years, different solutions have been tested in attempts to overcome "chemoresistance", including adding multiple agents (in combination and sequential regimens), by increasing dose intensity (high dose chemotherapy with bone marrow transplantation, sequential dose intense therapy) and by adding more effective agents (new chemotherapy agents, biologicals) [see Figures 6 and 7]. Dr de Boer believes that dose-dense therapy feeds into the concept that hormone-positive and hormone-negative cancers are different entities and that hormone-negative cancers are marked by high proliferation; such tumours should be ideal candidates for dose-dense therapy.

CALGB 9741

This pivotal trial in women with node-positive breast cancer evaluated sequential ATC compared with concurrent AC followed by paclitaxel, and also dose-dense (every 2 weeks with GCSF support) compared with conventional (every 3 weeks) scheduling. Long-term follow-up results confirm the superiority of the shortened inter-treatment interval of chemotherapy in terms of DFS and OS, in addition to being associated with less neutropenic sepsis, but with more anaemia.[25] Notably, dose-dense therapy favoured the subset of HR-negative tumours, whereas the type or frequency of chemotherapy schedule did not influence either DFS or OS in HR-positive tumours.

G-CSF maintains the dose-dense schedule

Granulocyte-colony stimulating factor (G-CSF) was essential for maintaining the every-2-weeks chemotherapy schedule in the CALGB 9741 trial. A phase 2 trial subsequently explored the use of pegfilgrastim and darbepoetin alfa, each given every 2 weeks, in support of every-2-weeks chemotherapy for stage I–III breast cancer.[26] With this schedule, absolute neutrophil counts were not problematic and were consistent with short-acting filgrastim given on days 3 through 10 of each cycle for the same chemotherapy regimen given in CALBG 9741. The toxicities were evenly spread between the schedules and were consistent with those reported in CALGB 9741.

Dr de Boer's only reservation with the dose-dense schedule is its relentless nature, whereas the every-3-weeks schedule allows patients to experience a greater level of recovery by week 3.

GONO MIG1 study

This Italian trial similarly investigated dose-dense therapy, in an evaluation of 6 courses of FEC chemotherapy given in accelerated fashion compared with the conventional approach.[27] The results do not provide equivocal support – a trend to a modest advantage was observed for every-2-weeks therapy in event-free survival and death, without reaching statistical significance [see Figure 8]. Notably, in an underpowered subset analysis, most of the benefit appeared to be in patients <50 years of age or whose tumours were ER-negative, or HER2-positive or had higher proliferation markers.

Dr de Boer suggests that in the light of these results, the dose-dense 2-weekly schedule may have a role to play in those more aggressive, rapidly proliferating tumours. He uses dose-dense chemotherapy primarily in patients with triple-negative disease.

Whilst trastuzumab is a critical treatment suitable for hormone-negative HER2-positive tumours. Dr de Boer has not yet resolved whether such tumours would be best treated by adjuvant trastuzumab combined with dose-dense therapy or with the more standard 3-weekly approach. Research conducted by the Memorial Sloan-Kettering Cancer Center indicates that this treatment is safe, with low cardiac toxicity. As dose-dense therapy is apparently of no particular benefit for hormone-positive tumours, Dr de Boer does not recommend such treatment for these patients, unless the shorter treatment time would be an advantage.

More clinical trial evidence would be useful to confirm the benefits of dose-dense therapy. A question that remains unanswered for Dr de Boer is whether the benefit is due to "dose-dense" treatment, or a more optimal scheduling of paclitaxel.

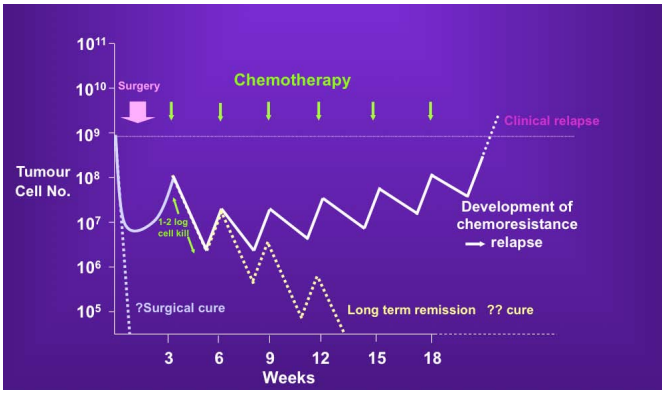

Figure 6. Adjuvant chemotherapy in breast cancer

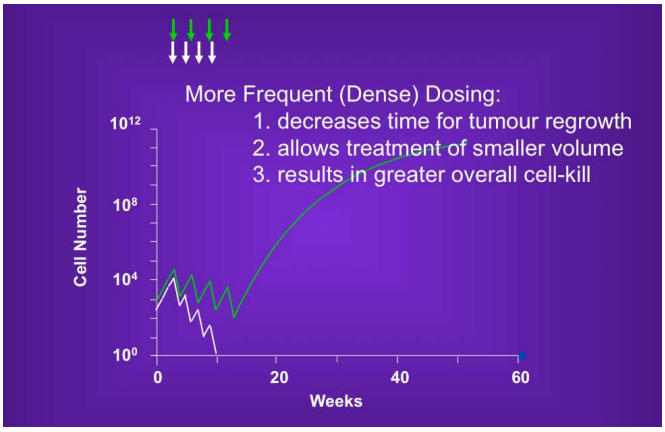

Figure 7. Dose-dense therapy in breast cancer

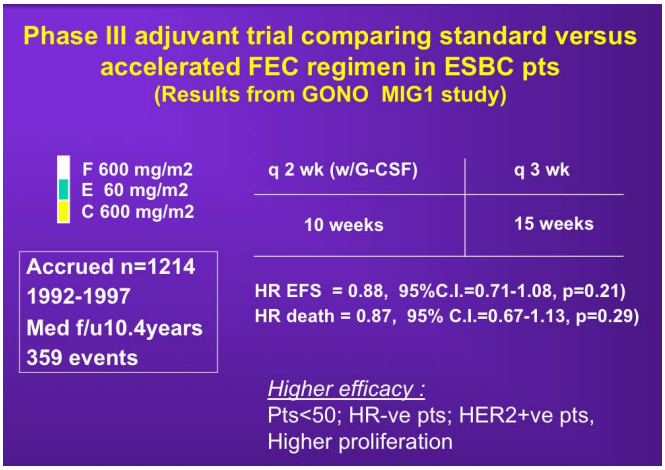

Figure 8. Results from the GONO MIG1 study[25]

NSABP B-38

Important results are expected from the NSABP B-38 trial, which has accrued almost 5000 patients with node-positive breast cancer. Three chemotherapy regimens are being compared: TACx6 every 3 weeks, ACx4-Px4 every 2 weeks and ACx4-PGx4 every 2 weeks [see Figure 9]. Will the dose-dense AC-P regimen prove superior to the TAC regimen and what impact does the addition of gemcitabine have in the adjuvant setting? What will the outcomes be for hormone receptor subgroups?

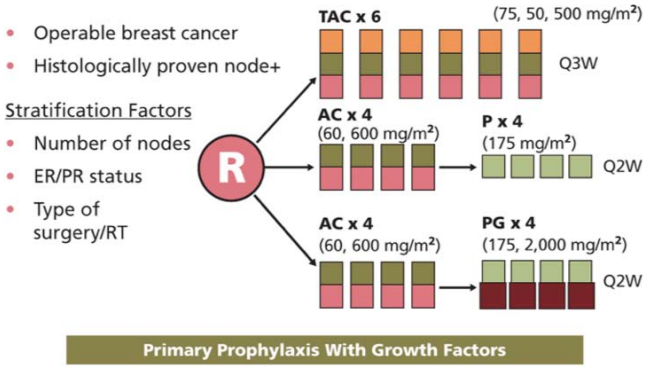

Figure 9. NSABP B-38: Combination taxane chemotherapy vs dose-dense sequential therapy

Which node-negative patients can be considered high risk?

Dr de Boer emphasised that triple-negative patients can often be lymph node-negative, but should still be considered to be of high risk. Unfortunately, many of the major adjuvant chemotherapy trials that established the taxane-based regimens were conducted in exclusively lymph node-positive patients. This has resulted in the erroneous idea that nodal status is the only marker of risk. As of late 2009 PBS prescribing rules in Australia limited taxanes to node-positive patients in the HER2-negative setting. Thankfully, there are increasing numbers of trials including higher risk node-negative patients in the adjuvant setting.

USON 9735: 7-year follow-up

In this pivotal study, patients with early breast cancer received either standard-dose AC (60/600 mg/m^2) or TCx4 (75/600 mg/m^2) every 3 weeks. At a median 7 years' follow-up, the difference in DFS between TC and AC was significant (81% TC vs 75% AC) as was OS (87% TC vs 82% AC). TC was superior in older patients as well as younger patients and there was no interaction of hormone-receptor status or HER-2 status and treatment.[16]

Data such as these draw attention to the TC regimen as being important for higher risk node-negative patients, in Dr de Boer's opinion.

Unresolved clinical questions

Despite many clinical trials there are still critical unresolved questions:

Which patients do *not* need chemotherapy? Perhaps the molecular signatures will provide insight (MINDACT, TAILORX).

Which patients do *not* need anthracyclines?

Which is the optimal taxane-based chemotherapy regimen?

Where does dose-dense chemotherapy fit?

Which cytotoxic agent is the best partner for targeted therapy (and which targeted therapy/ies)?

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