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De-escalating and escalating systemic therapy of early breast cancer

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1. Introduction

Despite a rising incidence of breast cancer internationally, breast cancer mortality started to fall from the 1980s onwards in all developed countries [1]. Improvements in adjuvant medical therapies have undoubtedly played a major part. Many more women than in the past have therefore survived breast cancer and issues of quality of life and the avoidance of long-term morbidities are increasingly important. Breast cancer specialists therefore need to evaluate carefully the extent to which the intensity or duration of medical therapies can be reduced without adversely influencing survival.

2. Adjuvant chemotherapy

Adjuvant chemotherapy for breast cancer is probably more unpleasant and toxic than for any other major cancer. Yet the history of trial design has trended strongly towards adding rather than reducing treatments. Non-inferiority trials of less treatment are uncommon and usually more difficult to fund than trials investigating the addition of new drugs.

2.1. Anthracyclines

Anthracyclines have been the mainstay of adjuvant chemotherapy for decades and have saved an enormous number of lives but they carry a significant risk of dose- and duration-related cardiotoxicity and leukaemia.

In Europe epiribucin is the standard treatment, usually at a dose of 90–100 mg/m^2 for 6 courses and sometimes more. The main adjuvant dose response data come from the FASG05 trial comparing epirubicin 50 mg/m^2 with 100 mg/m^2 x 6 courses in combination with 5FU and cyclophosphamide. This trial showed that 50 mg/m^2 was suboptimal with a significant benefit in favour of 100 mg/m^2 for both 10-year disease free survival and overall survival [2]. It is however by no means certain that there is a linear dose response curve between 50 and 100 mg/m^2 and it could well be that an intermediate dose of say around 75 mg/m^2 was as effective as higher doses. Evidence to support this comes from a dose escalation trial with doxorubicin in which 60 mg/m^2 was as effective as 75 mg/m^2 or 90 mg/m^2 $\times$3 weekly $\times$4 with significantly less toxicity [3]. However, a small phase II study (n = 51) comparing dose dence FEC90 to dose dense FEC75 showed an apparent reduction in risk of relapse with FEC90 (3.8% compared to 20% after a mean duration of follow-up of 3 years) [4]. European breast cancer specialists should address this question with a large randomised trial, since a lower dose would have significantly less short- and long term toxicities.

The duration of anthracycline therapy is another important issue. These are usually given for 6 courses if without subsequent taxanes, but a large trial, CALGB40101, showed that 4 cycles of standard AC chemotherapy at 3-week intervals were as effective as 6 in terms of both relapse free and overall survival. These patients had relatively good prognosis: 94% had node negative cancers but balanced against this, 47% had grade 3 tumours [5]. This trial also compared AC with paclitaxel and found AC to be significantly superior [6]. The difference was fairly small however: the 5 year relapse-free survival difference was 3% and the overall survival difference was 95% versus 94%. The AC arm was associated with 7 deaths from acute myeloid leukaemia/myelodysplastic syndrome and 2 from cardiac events compared with none with paclitaxel. Short duration (4 course) AC chemotherapy should be used rather than more prolonged duration treatment where chemotherapy is deemed appropriate for moderate risk patients. Such patients should likewise be offered the option of weekly paclitaxel as a generally less toxic alternative to AC and with only a small degree of inferiority [6].

The final anthracycline-related question is whether these agents are needed at all in an era when we have taxanes. This was addressed by joint analysis of 3 trials comparing taxane and cyclosphosphamide versus AC and a taxane. Four thousand two hundred and forty-two patients with HER2 negative cancer but high risk disease were included. The addition of anthracyclines significantly improved 4-year invasive disease-free survival by a

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small amount (90.7% versus 88.2%) but had no effect on 4-year overall survival (95% versus 94.7%) [7]. There was no significant gain for patients who were ER positive or node negative. Five patients treated with anthracyclines developed leukaemia versus none with TC. Consideration should therefore be given to avoiding anthracyclines completely in patients with ER positive, node negative breast cancer, and particularly in older patients with more risk of cardiac toxicity.

2.2. 5FU

5FU has been a component of adjuvant chemotherapy since the development of CMF. Recently however a trial comparing EC-paclitaxel to 5FU/EC-paclitaxel involving 2091 patients showed no improvement with 5FU in 5 year disease free survival (78% versus 79%) or overall survival (91% versus 92%); furthermore 5FU was associated with significantly more grade 3–4 neutropenia, fever, nausea and vomiting [8]. We should stop using 5FU routinely as adjuvant treatment for early breast cancer.

2.3. Carboplatin in triple negative disease

The GeparSixto randomised Phase 2 study in 51 German centres/595 patients with confirmed triple negative or HER2 positive breast cancer and at least T2 or node positive disease were randomised to carboplatin or not with paclitaxel and non-pegylated liposomal doxorubicin prior to surgery. Three-year disease free survival (DFS) was significantly improved for the 315 randomised patients with triple negative breast cancer (85.5 versus 76.1%, HR 0.56 95%CI, 0.33–0.96, P0.35), but not for patients with HER2 positive disease [9]. PathCR was numerically but not statistically higher in patients with germline *BRCA* mutations treated with carboplatin (61.5% versus 50.5%, p = NS), but there was no significant benefit for DFS in this small subgroup (n = 50), In contrast, a trial comparing carboplatin with docetaxel as first line treatment for metastatic triple negative breast cancer (TNT: Triple Negative Trial) showed a significant progression-free survival only for patients with *BRCA* mutations but not otherwise [10]. Neoadjuvant carboplatin cannot at present therefore be recommended for triple negative breast cancer except for patients with co-existent *BRCA* mutations.

2.4. Adding capecitabine in triple negative breast cancer

The FinnX trial involved 1500 patients randomised to docetaxel 80 mg/m^2 ×3 courses followed by FEC chemotherapy ×3 courses with or without additional capecitabine 900 mg/m^2 twice daily days 1–14 every 21 days. The addition of capecitabine had no overall benefit, but did show a very significant improvement in recurrence-free survival for patients with triple negative breast cancer (HR 0.53, 95%CI, 0.31–0.92 P0.02) [11].

Supporting this, the CREATE-X trial randomised 910 patients with HER2 negative breast cancer who failed to achieve a pathCR and were node positive after neoadjuvant chemotherapy to capecitabine (2500 mg/m^2/day days 1–14 q 21 days) up to 8 cycles, or not post-operatively. This trial showed a significant 5-year disease-free survival benefit (74.1 versus 67.7%, HR 0.70, p = 0.00524) and overall survival benefit (89.2 versus 83.9%, HR 0.60, p < 0.01) for capecitabine, with the most marked benefit for 296 patients who had ER negative cancers (HR 0.58 90%CI, 0.39–0.87). The equivalent figures for patients with ER positive cancers were HR 0.84, CI 0.57–1.23) [12]. Results of this trial have recently been published, but there are earlier data failing to support these results. Nevertheless these trials suggest that there may well be an advantage of adding capecitabine to the treatment of triple negative breast cancer, particularly if neoadjuvant chemotherapy has failed to achieve a pathological complete remission. A confirmatory trial addressing this important question is warranted.

3. De-escalating chemotherapy for HER2 positive early breast cancer

A large non-randomised trial (APT) run in the Eastern USA treated 406 patients with small (less than 3 cm) node negative (or 1 micrometastasis), HER2 positive cancers with weekly paclitaxel 80mg/m^2 for 12 weeks, instead of more intensive standard chemotherapy, along with trastuzumab 3 weekly for 1 year. With a median follow-up of 4 years the 3-year invasive disease-free survival was 98.7% with only 2 distant relapses (0.4%) [13]. These results are so impressive that this treatment has rightly become standard for small HER2-positive breast cancers even in the absence of a control arm. Furthermore, it seems extremely likely that at least some patients with larger breast cancers could also benefit from this de-escalated chemotherapy with much less toxicity than standard.

With the advent of pertuzumab in addition to trastuzumab, the Phase 2 NeoSphere trial which involved 417 patients with operable (>2 cm) or locally advanced breast cancer showed that the addition of pertuzumab to conventional docetaxel and trastuzumab very significantly improved pathological complete remission rate particularly in patients with ER negative breast cancer (63.2% versus 26%). Interestingly, 27.3% of ER negative, HER2 positive patients treated with pertuzumab and trastuzumab alone achieved a complete pathological remission [14]. Subsequent follow-up confirmed that patients achieving a pathCR did significantly better in terms of 5-year progression-free survival than those who did not [15].

More recently, the KRISTINE neoadjuvant trial involved 444 patients with HER2 positive breast cancer randomised either to standard docetaxel, carboplatin, trastuzumab and pertuzumab or to the novel combination of TDM1 and pertuzumab. The conventional chemotherapy-containing arm achieved a significantly higher pathCR (56%) than the TDM1 pertuzumab arm (44%) The equivalent figures for patients with ER negative breast cancer were 73% versus 54%.

Nevertheless the pathCR rate for the novel combination of TDM1 with pertuzumab was impressive (54% in patients with ER-ve cancers) and was achieved with a very significant reduction in side effects, improvement in quality of life and maintenance of physical function [16]. These trials further demonstrate that a significant number of patients with HER2 positive breast cancer do not need intensive conventional chemotherapy with the advent of anti-HER2 targeted therapies.

So far attempts to identify tumour markers which predict which patients can achieve a pathCR with minimal, or no chemotherapy have failed [17,18]. However a way forward could be with a neo-adjuvant approach, in which all patients with HER2 positive breast cancer are treated initially with dual anti-HER2 targeted treatment and with limited (eg weekly paclitaxel) or no chemotherapy. Those achieving a pathCR would continue on the same anti-HER2 therapy without chemotherapy; those failing to achieve a pathCR could have post-operative adjuvant standard chemotherapy. (Fig. 1). This design does of course beg the question of whether all pathCR are the same in terms of outcome and a way to address to this question would be to randomise the no-chemotherapy pathCR arm to subsequent adjuvant chemotherapy or not.

4. Genomic platforms

Genomic platforms based on selective gene expression within

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