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Current and future directions for adjuvant chemotherapy in early-stage breast cancer

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1. Introduction

In recent years, there has been a considerable improvement in patient outcomes after chemotherapy in early-stage breast cancer. In addition to the significant improvements in surgery, radiotherapy, screening, time to diagnosis, and the use and delivery of adjuvant hormonal and chemotherapy, the introduction of the taxoids – docetaxel and paclitaxel – has played an important role in this improvement. In addition, improvement in our understanding of molecular genomics has resulted in advances in the identification of different breast cancer subtypes. With this increased knowledge of both the disease and its treatment, it is timely to ask the question: what is the gold standard for adjuvant chemotherapy in 2005?

In attempting to answer this question, it is important to begin with the evolution of adjuvant chemotherapy. It is well known that the first regimen used in this setting was a triple therapy (CMF) comprising cyclophosphamide, methotrexate and 5-fluorouracil (5-FU). Using CMF, patients experienced a reduction in the risk of death of approximately 14% compared with surgery alone [1]. The inclusion of anthracyclines in adjuvant treatment resulted in the development of three main anthracycline-based combination regimens – (i) doxorubicin and cyclophosphamide (AC), (ii) 5-FU, epirubicin and cyclophosphamide (FEC); and (iii) 5-FU, doxorubicin and cyclophosphamide (FAC). The reduction in risk of death achieved with these combinations was of a similar order to that obtained with CMF, at approximately 11% [1].

The next major advance in the delivery of adjuvant cytotoxic chemotherapy was the addition of taxoids, either in combination with or in sequence after anthracycline-based treatment. In the USA, two studies – the Cancer and Leukemia Group B (CALGB) 9344 study [2] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 study [3] – were conducted to investigate the addition of sequential paclitaxel to AC. In Europe, the French Adjuvant Study Group (FASG), having established the FEC100 regimen as the reference treatment for early-stage, node-positive breast cancer, conducted the PACS 01 trial, in which the last three cycles of $FE_{100}C$ were substituted with three cycles of sequential docetaxel [4]. The Breast Cancer International Research Group (BCIRG) 001 (TAX 316) trial studied the effects of substituting 5-FU in the FAC regimen with docetaxel, producing the TAC regimen [5]. Finally, the Spanish GEICAM 9906 [6] and the US Oncology 9735 [7] trials, the results of which were presented at the 2005 San Antonio Breast Cancer Symposium (SABCS), reported the addition of paclitaxel in sequence after, or the inclusion of docetaxel in place of, anthracyclines. A number of other second-generation studies have investigated the optimal delivery of taxoid-based schedules, including the CALGB/Intergroup C9741 trial and the Eastern Co-operative Oncology Group (ECOG) 1199 study. The CALGB/Intergroup C9741 study investigated, in a two-by-two design, the role of dose-dense versus conventional 3-weekly paclitaxel, and also sequential versus concurrent therapy [8]. The ECOG 1199 is a four-arm study that directly compared docetaxel versus paclitaxel in sequence following AC, and also weekly versus 3-weekly therapy [9]. The results of these trials have cemented the position of the taxoids as state-of-the-art care for patients with node-positive early-stage breast cancer.

2. Trials assessing the addition of a taxoid to conventional chemotherapy

The CALGB 9344 study randomised 3121 patients with node-positive, operable breast cancer to receive either four cycles of cyclophosphamide (600 mg/m^2) in combination with one of three doses of doxorubicin (60, 75 or 90 mg/m^2) every 3 weeks, followed by either no further therapy or four cycles of 3-weekly paclitaxel at 175 mg/m^2. Most patients (94%) were hormone-receptor positive and, as such, received tamoxifen therapy following completion

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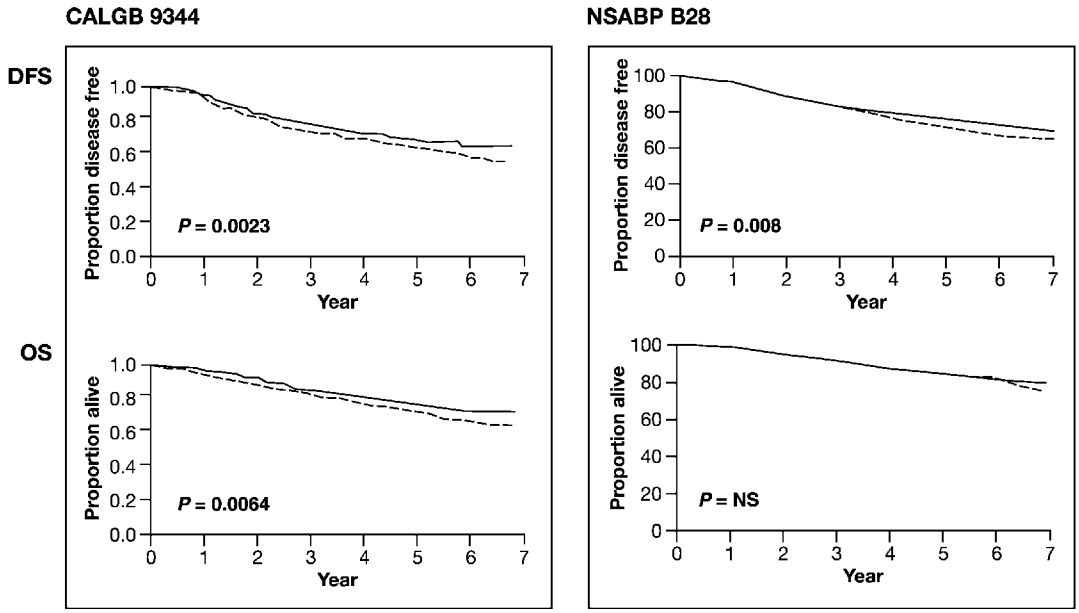

Fig. 1. Efficacy results of paclitaxel trials.

of chemotherapy [2]. In the NSABP B28 trial, 3060 patients were randomised to receive either four cycles of AC (cyclophosphamide 600 mg/m^2/doxorubicin 60 mg/m^2) or four cycles of AC followed by four cycles of paclitaxel at the increased dose of 225 mg/m^2. All patients over the age of 50 years, and those younger than 50 who had hormone-receptor-positive tumours, received tamoxifen concurrently with their chemotherapy for 5 years [3]. Both trials have mature, long-term follow-up and are now published. In the CALGB 9344 study, the addition of paclitaxel resulted in significant increases in both disease-free survival (DFS) and overall survival (OS) compared with AC, producing a 17% relative reduction in the risk of recurrence and an 18% reduction in the risk of death (Fig. 1) [2]. The results from NSABP B28, however, were not entirely consistent with those of the CALGB 9344 study. While the addition of paclitaxel to AC produced a significant reduction in the risk of recurrence that was similar to that demonstrated in the CALGB 9344 study, it did not produce a singnificant improvement in OS (Fig. 1) [3]. There are potential reasons for this discrepancy, including the fact that the population studied in the NSABP B28 study had a better prognosis than the group of patients studied in the CALCG 9344 trial and the concurrent tamoxifen use in the NSABP B28 trial may have abrogated the size of the taxoid benefit.

Six cycles of the $FE_{100}C$ regimen is currently the most commonly used reference adjuvant therapy in Europe. A number of trials have investigated the benefits of the addition of taxoid sequential therapy to FEC regimens. The GEICAM 9906 study randomised 1248 patients with node-positive, operable breast cancer to receive either six cycles of $FE_{90}C$ (5-FU 600 mg/m^2/epirubicin 90 mg/m^2/cyclophosphamide 600 mg/m^2, every 3 weeks) or four cycles of the same schedule followed by eight weekly doses of paclitaxel (100 mg/m^2). An interim analysis performed at a median of 47 months revealed a significant increase in 4-year DFS for the paclitaxel arm compared with FEC alone (85.0% versus 79.0%; $P = 0.008$), although given the small size of the study, this did not translate into a significant increase in OS (94.0% and 92.4%, respectively: $P = 0.14$). Subset analysis revealed that the $4FE_{90}C$–8P regimen demonstrated improved efficacy compared with $6FE_{90}C$ in both ER-positive and ER-negative populations. Although this benefit was observed in all patients, the magnitude of effect was greater in patients with ER-negative disease [6].

The efficacy of sequential docetaxel following the FEC regimen was investigated in the PACS 01 trial, which compared six cycles of 3-weekly $FE_{100}C$ with three cycles of 3-weekly $FE_{100}C$ followed by three cycles of 3-weekly docetaxel at 100 mg/m^2 ($3FE_{100}C$–3T) in 1999 women [4]. Patients with hormone-receptor-positive tumours were prescribed daily tamoxifen treatment for 5 years following completion of chemotherapy. Patients in the docetaxel arm experienced a significant increase in both DFS and OS compared with those who received $FE_{100}C$ only. The probability of DFS was increased from 73.2% in the $6FE_{100}C$ group to 78.3% in the $3FE_{100}C$–3T group, which corresponded to a 17% relative reduction in the risk of relapse. Compared with $6FE_{100}C$, the $3FE_{100}C$–3T regimen produced a significant increase in OS of 4% (from 86.7% to 90.7%) which corresponded to a 23% relative reduction in the risk of death [4]. Subgroup analysis revealed that compared with the $6FE_{100}C$ regimen, the $3FE_{100}C3$–3T regimen produced a significantly better outcome in patients with 1–3 positive nodes ($P = 0.042$; hazard ratio [HR] = 0.76 [95% CI: 0.58–1.00]), but not $\geqslant 4$ positive nodes ($P = 0.120$; HR = 0.87 [95% CI: 0.68–1.11]). The $3FE_{100}C$–3T regimen significantly improved DFS in patients of

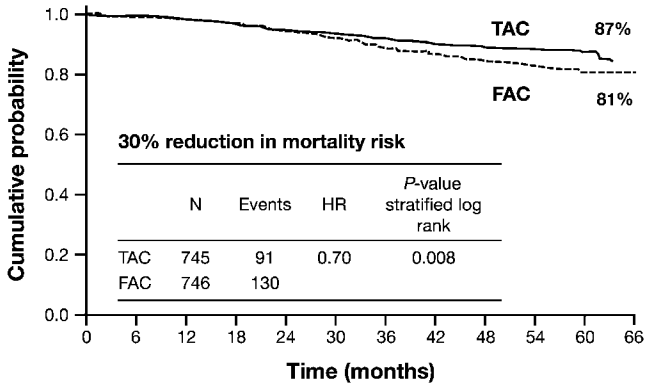

Fig. 2. BCIRG 001: overall survival (ITT).

age 50 years or over ($P = 0.001$; HR = 0.67 [95% CI: 0.51–0.88]), but not in those younger than 50 years of age ($P = 0.69$; HR = 0.98 [95% CI: 0.77–1.25]) [4].

Only one published trial has so far confirmed a benefit for the use of a taxoid in combination therapy compared with anthracycline treatment alone. The BCIRG 001 trial investigated the outcomes of using docetaxel in combination with AC (TAC) and was recently published after a median of 55 months of follow-up [5]. In this study, 1491 women with axillary node-positive breast cancer were randomised to receive six cycles of treatment with either FAC or TAC as adjuvant chemotherapy after surgery. The primary endpoint was DFS, and secondary endpoints were OS, toxicity and quality of life. Patients in both arms of this study received the same concentrations of doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2), with patients in the TAC arm receiving 75 mg/m^2 docetaxel in place of 5-FU. Intent-to-treat (ITT) analyses revealed that patients in the docetaxel (TAC) arm had a cumulative probability of DFS of 75% compared with 68% for patients who received FAC. This 7% absolute increase was statistically significant at the 0.001 level and corresponded to a 28% relative reduction in the risk of relapse. Similarly, patients who received TAC experienced a 6% absolute increase in probability of OS, which was 87% compared with 81% for patients in the FAC group. Again, this difference was statistically significant ($P = 0.008$) and corresponded to a 30% relative reduction in the risk of death (Fig. 2) [5]. The superiority of TAC over FAC was also observed in all planned subgroup analyses, which included the number of involved axillary lymph nodes, ER status, and human epidermal growth factor 2 (HER2)/neu status, and was independent of menopausal status [5].

Three other trials that were designed to assess the role of taxoids in addition to anthracyclines are closed but have not yet reported. The UK Taxotere®as Adjuvant Chemotherapy trial (TACT) assessed 4162 patients with completely resected node-positive or high-risk node-negative breast cancer. Patients were randomised to receive either eight cycles of FEC/four cycles of epirubicin followed by four cycles of CMF (ECMF) or four cycles of FEC followed by four cycles of docetaxel. The National Cancer Institute of Canada (NCIC) Clinical Trials Group MA.21 study compared six cycles of FEC with sequential therapy comprising four cycles of EC followed by four cycles of paclitaxel, or the same regimen delivered in a dose-dense fashion. Finally, the Breast International Group (BIG) 02-98 trial will assess the addition of docetaxel versus no treatment after either AC–CMF or A–CMF in a four-arm design. These three large trials will be invaluable in clarifying the role of taxoids in adjuvant therapy.

3. Second-generation taxoid trials

The Intergroup/CALGB C9741 study is a two-by-two study in 2005 patients with node-positive disease that was designed to investigate the safety and efficacy of sequential versus concurrent AC therapy followed by paclitaxel and also, the outcomes of using both regimens, either as the standard 3-weekly regimen or as a dose-dense regimen (every 2 weeks with granulocyte colony-stimulating factor [G-CSF]) [8]. The final analysis has been performed after 6.5 years' follow-up, the results of which demonstrate that dose-dense treatment produced a significant increase in DFS compared with 3-weekly treatments ($P = 0.012$), resulting in a 25% reduction in the risk of relapse. While the study continues to suggest an improvement in OS for dose-dense therapy compared with the standard q3w therapy (HR = 0.85; $P = 0.049$) this is markedly less than that observed at the time of the original report [10] and is only just statistically significant. As with the CALGB 9344 study, subgroup analysis suggests that the DFS and OS advantages only occur in patients with ER-negative disease. There was no significant difference in DFS or OS for concurrent regimens compared with sequential regimens.

The ECOG E1199 study is a large four-arm study conducted in 5052 patients with operable Stage II or IIIA, axillary node-positive or high-risk node-negative breast cancer, which was designed to determine the most active taxoid and schedule [9]. Patients were randomised to receive sequential therapy of either four cycles of 3-weekly paclitaxel (175 mg/m^2; control arm), 12 cycles of weekly paclitaxel (80 mg/m^2), four cycles of 3-weekly docetaxel (100 mg/m^2), or 12 cycles of weekly docetaxel (35 mg/m^2) following four 3-weekly cycles of AC (doxorubicin 60 mg/m^2/cyclophosphamide 600 mg/m^2). Treatment with G-CSF was permitted in this trial. The primary endpoint of the study was DFS at 5 years, and the predefined primary analyses were to compare the pooled data from patients treated with paclitaxel with those treated with docetaxel and to compare the pooled data from patients who received a weekly schedule with those from patients who received a 3-weekly schedule. Exploratory secondary analyses assessed whether any of the other three regimens were superior to the 3-weekly paclitaxel regimen. The results of this study, based on data available from 4988 patients at a median follow-up of 46.5 months

and a total of 856 DFS events and 483 deaths, were recently reported at the 2005 SABCS meeting. These results demonstrated no significant differences in DFS between either the taxoid (HR = 0.99; $P = 0.83$), or between weekly and 3-weekly schedules (HR = 1.04; $P = 0.54$). There was a trend favouring weekly paclitaxel over 3-weekly paclitaxel. However, patients in the weekly paclitaxel arm received a 37% higher total dose than those in the 3-weekly paclitaxel arm. An unplanned analysis revealed that there were approximately 15% fewer relapses with 3-weekly docetaxel and the weekly paclitaxel schedules, compared with the 3-weekly paclitaxel schedule. The event rates were lower than expected in this study, and although the study was powered for analysis at 1400 events, the data were released at 856 events. Further analyses are planned after 1042 and after 1400 events and will provide a more definitive evaluation.

Efficacy results from two further trials comparing different taxoid schedules are awaited. The NSABP B38 trial randomised patients with histologically proven node-positive breast cancer to receive either six cycles of 3-weekly TAC, four cycles of 2-weekly AC followed by four cycles of 2-weekly paclitaxel, or four cycles of 2-weekly AC followed by four cycles of 2-weekly paclitaxel plus gemcitabine. The relative efficacy and safety of combination and sequential therapy with docetaxel is currently being assessed in the BCIRG 005 trial [11]. In this trial, 3130 patients with node-positive, HER2-negative disease were randomised to receive either sequential therapy comprising four cycles of 3-weekly AC followed by four cycles of 3-weekly docetaxel (100 mg/m^2; AC–T arm), or six cycles of 3-weekly TAC. Prophylactic antibiotics and ciprofloxacin were administered to patients who received TAC, and tamoxifen was administered to patients with hormone-receptor-positive disease. Safety results were reported after a median follow-up of 30 months and 392 DFS events. The safety profiles were generally similar in each arm, although there was an increased incidence of febrile neutropenia in the TAC arm compared with the AC–T arm (17.9% versus 8.5%, respectively) and an increased incidence of neurotoxicity and myalgia in the AC–T arm compared with the TAC arm. As yet, efficacy data on these trials are not available.

4. Non-anthracycline taxoid combinations

It has long been known that the use of anthracyclines is associated with a significant increase in the risk of cardiotoxicity. As such, a number of trials have investigated the potential of non-anthracycline-containing regimens. In the metastatic setting, the TC doublet (docetaxel 60 mg/m^2/cyclophosphamide 600 mg/m^2) has proved to be efficacious without associated cardiac toxicity. The efficacy and safety of this regimen has now been investigated in the adjuvant setting in 1016 patients with Stage I, II or operable Stage III invasive breast cancer [7]. Eligible patients were randomised to receive four 3-weekly cycles of either standard-dose AC (doxorubicin 60 mg/m^2/cyclophosphamide 600 mg/m^2; $n = 510$) or TC ($n = 506$). The 5-year DFS rate was significantly increased with TC compared with AC (86% versus 80%; $P < 0.015$) with a reduction in the risk of recurrence of 33%. The difference in OS between the treatment arms is not yet statistically significant, but there is a trend in favour of TC, and the current HR is 0.76. On the basis of these data, the TC regimen – which produced a longer DFS compared with standard AC and was the better-tolerated adjuvant regimen – could be considered as a standard therapy alternative to replace the AC regimen in patients with low-risk early-stage breast cancer.

Another trial incorporating a non-anthracycline standard arm is the BCIRG 006 trial [12]. In this three-arm study, node-positive and high-risk node-negative, HER2-positive patients were randomised to receive either four cycles of AC followed by six cycles of docetaxel (100 mg/m^2; AC–T), four cycles of AC followed by four cycles of docetaxel plus 1 year of trastuzumab therapy (AC–TH), or a non-anthracycline-containing regimen comprising docetaxel (75 mg/m^2), carboplatin (AUC 6) and trastuzumab (4 mg/kg loading dose followed by 2 mg/kg for 1 year; TCH). The interim results are based on 322 events after a median follow-up of 23 months. The 4-year DFS rates were 73%, 80% and 84% for the AC–T, AC–TH and TCH regimens, respectively. Compared with the AC–T control arm, the trastuzumab-containing regimens were associated with significantly increased DFS, represented by reductions in the risk of relapse of 51% ($P = 0.0000005$) and 39% ($P = 0.000153$) for the AC–TH and TCH arms, respectively. There is, at this stage, no statistically significant difference in DFS between the two trastuzumab-containing regimens ($P = 0.16$). The secondary endpoint of OS has not yet been reached. All three regimens were well tolerated and more than 90% of the planned therapy was administered. There was no statistically significant difference in the incidence of febrile neutropenia or neutropenic infection in any of the arms, and all three regimens appear to be safe and manageable regarding non-haematological toxicities. Compared with the AC–T control arm, the incidence of cardiac events was significantly increased in the AC–TH arm (0.95% for AC–T versus 2.34% for AC–TH; $P = 0.016$), but not in the TCH arm (0.95% for AC–T versus 1.33% for TCH; $P = 0.54$). The rate of >10% relative left ventricular ejection fraction (LVEF) decline was significantly increased in the AC–TH arm (17.3%) compared with the AC–T (9.0%) and TCH (8.0%) arms ($P = 0.002$ and $P < 0.0001$, respectively; Fig. 3). The incidence of >10% LVEF decline in the TCH group did not differ significantly from the AC–T group ($P = 0.493$). A separate analysis revealed that approximately 35% of patients who were randomised had an amplification of the gene encoding topoisomerase (topo) II alpha. Early studies have suggested that this amplification may confer

a therapeutic advantage to anthracycline-based trastuzumab regimens. As such, non-anthracycline-based chemotherapy regimens, such as TCH, may be particularly useful in HER2-positive patients without co-amplified topo II, as well as in patients who have cardiac comorbidities.

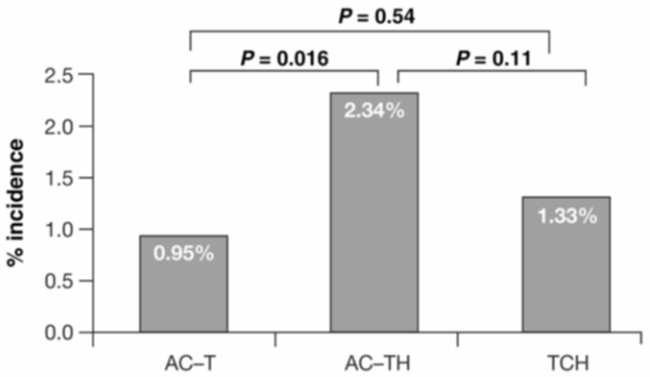

Fig. 3. BCIRG 006: cardiac safety.

5. The benefit of growth factor therapy

The results of the BCIRG 001 and PACS 01 trials clearly demonstrate the efficacy advantages of including docetaxel in adjuvant therapy. However, as is the nature of chemotherapy, toxicities exist, and these also need to be considered. The main toxicities associated with the TAC regimen are myelosuppression and associated febrile neutropenia. In the BCIRG 001 trial, nearly 25% of patients in the TAC arm had an episode of febrile neutropenia, compared with 2.5% in patients who received FAC. However, there was only a slight and non-significant increase in the incidence of infections (Grade 3/4 or severe), from 2.2% in patients in the FAC arm to 3.9% in patients who received TAC [5]. The development of febrile neutropenia has important clinical and resource implications in everyday clinical practice. Strategies exist that can be employed to prevent the development of febrile neutropenia, thereby improving patients' access to the most efficacious regimens. The reduction of TAC-induced febrile neutropenia achieved by the use of prophylactic G-CSF was effectively demonstrated by a protocol amendment in the GEICAM 9805 study [13]. This trial had exactly the same design as BCIRG 001 but studied node-negative patients. The protocol amendment permitted the use of prophylactic G-CSF from the first cycle, in all patients in the TAC arm. The use of prophylactic G-CSF resulted in a significant reduction in the per-patient incidence of febrile neutropenia owing to the administration of TAC, from 24.6% to 6.5%. Similarly, there was a significant decrease in the per-patient incidence of infections, from 31.6% in the pre-amendment population to 21.7% in the post-amendment population (Fig. 4).

These results clearly demonstrate the advantage of primary G-CSF prophylaxis in terms of febrile neutropenia. However, the GEICAM 9805 study also demonstrates that such practice is beneficial in reducing the incidence of asthenia, stomatitis and diarrhoea, and as such, demonstrates that with the use of prophylactic G-CSF, the toxicities associated with the TAC regimen become readily manageable. It is a reasonable assumption that, in order to maximise the efficacy potential of the TAC regimen, we should be routinely employing prophylactic G-CSF therapy in patients at risk of developing febrile neutropenia. The 2005 National Comprehensive Cancer Network (NCCN) guidelines recommend the use of prophylactic G-CSF support for regimens associated with a febrile neutropenia rate of more than 20% [14]. While the BCIRG 001 trial investigated the outcomes of a triplet combination therapy containing docetaxel, the PACS 01 trial employed sequential docetaxel. In the latter trial, the incidence of febrile neutropenia in the $3FE_{100}C$–3T arm was 11.2% versus 8.4% for the $6FE_{100}C$ arm [4]. Again, this percentage is deemed manageable and is below the rate of 20% as recommended by the NCCN, and as such, the $3FE_{100}C$–3T regimen offers an efficacious therapy with a low incidence of febrile neutropenia.

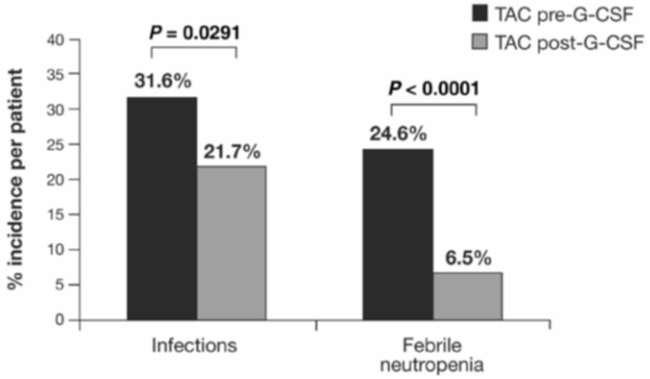

Fig. 4. Benefits of prophylactic G-CSF in the adjuvant setting.

6. Future trial design: the use of gene expression profiling

The ultimate goal of cancer therapy is to individualise treatment. We can now begin to define specific patient subgroups that will benefit from taxoid chemotherapy; for example, patients with a specific nodal status or hormone-receptor status or patients above a particular age. With our increased understanding of genomics and proteomics, oncologists are now asking whether it is possible to use molecular profiling to drive the design of adjuvant trials. We already have the tools that allow us to differentiate patients with different subtypes of breast cancer for trial entry, so can we therefore now use these tools to better identify patients who do not need adjuvant chemotherapy? One such large multinational trial is currently underway. A 70-gene microarray expression profile developed by a group of Dutch researchers clearly differentiated a group of patients with a very good prognosis who could potentially

be spared adjuvant chemotherapy. In two small retrospective studies, this new prognostic tool outperformed the St Gallen criteria [15,16]. These results have now been validated with a series of independent frozen tumour specimens in multiple validation sets across different microarray platforms [17] and have formed the basis for the Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial. This joint trial between the Breast International Group (BIG) and the European Organisation for Research and Treatment of Cancer (EORTC) aims to correlate genomic and clinical information, to determine which patients should receive chemotherapy and which should not. In cases where the genomic profile differs from the clinical profile, patients will be randomised to receive chemotherapy or no chemotherapy. This large and complex trial offers the opportunity to radically change the way patients with early-stage breast cancer are managed, both in the European Union and at a global level. Other studies have already begun to establish which subtypes of cancer will respond best to neoadjuvant chemotherapy. In a seminal paper, Rouzier and colleagues [18] used an *in vivo* model to determine whether the different molecular subtypes of breast cancer respond differently to preoperative chemotherapy. Fine-needle aspirations of 82 breast cancers were obtained before starting preoperative paclitaxel followed by FAC chemotherapy. The results of this study suggest that HER2-positive or basal-like subtypes of breast cancer are more sensitive to paclitaxel- and doxorubicin-containing preoperative chemotherapy, having a response rate of 45%, but that patients with luminal tumours would have only a 6% response to this chemotherapy.

7. Conclusion

The inclusion of taxoids in adjuvant therapy has produced unquestionable benefits for patients with early-stage breast cancer. Large randomised trials involving paclitaxel, and in particular docetaxel, demonstrate clear, clinically meaningful differences in OS. These benefits have been seen with both sequential and combination regimens. The largest absolute benefits in terms of OS seen to date are where docetaxel has been added to standard anthracycline regimens, either in combination (TAC; BCIRG 001) or sequence ($3FE_{100}C$–3T; PACS 01). Although the OS advantage associated with paclitaxel is not consistent, the optimal delivery schedule for this agent is still to be established. The NSABP B38 study will address this point through comparison of the TAC regimen with dose-dense doxorubicin/cyclophosphamide followed by dose-dense paclitaxel, and with dose-dense AC followed by dose-dense paclitaxel plus gemcitabine. Another study – the UK tAnGo trial – is a prospective, multicentre phase III evaluation of gemcitabine and paclitaxel versus paclitaxel as a single agent following epirubicin-based chemotherapy for higher-risk early-stage breast cancer.

The administration of prophylactic growth factors has also been shown to significantly reduce the incidence of febrile neutropenia that arises as a result of the administration of otherwise very effective regimens, such as TAC. Where cardiac toxicity is a concern, non-anthracycline regimens that incorporate docetaxel – for example the TC regimen (docetaxel, cyclophosphamide) or the TCH regimen (docetaxel, carboplatin, trastuzumab) for HER2-positive patients – can now be accepted as standard practice regimens. Taxoid-based therapy should now be considered the gold standard for node-positive disease, and is now actively being investigated in patients with high-risk, node-negative disease. Large trials such as the UK TACT trial, the BIG 02-98 trial and the NCIC MA 21 trial (in which the standard arm is the Canadian CEF, as opposed to the European FEC regimen) will further inform this field. Ongoing questions regarding cytotoxic therapies include whether the addition of agents such as capecitabine or gemcitabine will further improve the outcomes achieved thus far; however, it is envisaged that the real benefit of such combinations is likely to be small. The potential of combination therapies including novel therapeutics, for example targeted agents such as bevacizumab and lapatinib, may offer patients more potential for cure. Finally, the use of genomic/proteomic approaches is now being assessed in the adjuvant setting, and it is hoped that the information rendered from such studies will contribute greatly to the individualisation of therapy for patients with cancer.

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