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REVIEW ARTICLE

Adjuvant Chemotherapy for High-risk Node-positive Breast Cancer: a Tale of Three Generations

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ABSTRACT

Adjuvant chemotherapy for node-positive breast cancers has evolved a long way from the time-honoured non-anthracycline regimen of six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) to the historical standard of anthracycline-based regimens of either four cycles of AC (adriamycin, cyclophosphamide) or six cycles of FAC/FEC (5-fluorouracil, adriamycin/epirubicin, cyclophosphamide), and now to the third-generation taxane-based regimens. Before the advent of taxanes, attempts to dose-escalate the anthracycline did improve outcome for the FEC regimen, but not the AC regimen. The Milan regimen, consisting of 12 cycles of sequential adriamycin followed by CMF, has also gained popularity in Europe especially for high-risk patients with a substantial number of metastatic nodes. For a few years, in Hong Kong public hospitals taxanes have become available to high-risk node-positive patients (lymph node number, >3) at no extra costs. The published results of these taxane-based regimens in high-risk node-positive patients are reviewed. The results of a randomised phase 2 study for high-risk node-positive patients conducted in our institution before the taxane era, which compared the outcome and tolerance of the Milan regimen with the escalated FEC regimen (FE100C), are also briefly discussed with reference to the benefits of the current taxane-based chemotherapy.

Key Words: *Breast neoplasms; Chemotherapy, adjuvant*

中文摘要

淋巴結陽性乳癌的輔助化療：細説三代化學治療的故事

顏繼昌

高風險淋巴結陽性乳癌輔助化療的發展可以分為三代。從第一代不含蒽環類藥物（anthracycline）的CMF（環磷酰胺cyclophosphamide、甲氨蝶呤methotrexate、5-氟尿嘧啶5-fluorouracil，6個療程），到第二代含有蒽環類藥物的歷史標準如AC（阿霉素adriamycin、環磷酰胺，4個療程）或FAC/FEC（5-氟尿嘧啶、阿霉素／表阿霉素epirubicin、環磷酰胺，6個療程），發展至現在含有紫杉醇類（taxane）的第三代化療。在未出現紫杉醇類藥物之前，曾有不同嘗試藉著提高蒽環類藥物劑量來改善療效，可惜只有FEC方案可行，AC方案則未見改善。米蘭癌症研究所應用順序式阿霉素後再加上CMF共12個療程，這聯合方案已在歐洲普遍使用於那些高風險帶有大量淋巴結轉移的病人。香港公營醫院亦已為高風險淋巴結陽性乳癌患者（即淋巴結數目大於三）免費提供紫杉醇類療程達數年。本文回顧有關高風險淋巴結陽性乳癌患者接受紫杉醇類療程後臨床結果的文獻。此外，本院在未發展紫杉醇類藥

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物化療之前，曾為高風險淋巴結陽性乳癌患者進行一項隨機（二期）研究，比較使用米蘭癌症研究所的化療方案及另一個升級FEC方案（FE100C）的效果及耐受性。本文會根據現時紫杉醇類化療結果作為參考，討論這項隨機研究的結果。

INTRODUCTION

Breast cancer is the most prevalent female cancer worldwide, and is the leading cause of cancer mortality for women in developed countries. In 2009, 2945 new cases were diagnosed in Hong Kong and 555 women died of the disease, which ranked breast cancer as the first and third most common cause of female cancer incidence and mortality, respectively.[1] Indeed, breast cancer is generally regarded as a systemic disease that kills by distant metastases, and hence systemic adjuvant treatments like chemotherapy, hormone therapy, and targeted therapy for eligible patients constitute the key components in effective treatment.

The Expert Panel Consensus defines patients with four or more positive axillary lymph nodes as having high-risk breast cancer, for which adjuvant chemotherapy and other appropriate systemic treatments are strongly recommended.[2] The definition can be fully justified as patients with four or more positive axillary lymph nodes have a five-year overall survival (OS) of 50% or less.[3] Those patients with smaller numbers of positive lymph nodes (1-3) who have either hormone receptor (HR)–negative status or HER2/*neu* gene over-expression or amplification are also regarded as having high-risk disease that could benefit from adjuvant chemotherapy and / or trastuzumab therapy.[2] The subsequent discussion in this report on the use of various generations of adjuvant chemotherapy will focus on high-risk patients with four or more positive axillary lymph nodes, irrespective of their HR or HER2 status.

FIRST-GENERATION CHEMOTHERAPY

The 2005 meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the use of anthracycline combination chemotherapy of either FAC (fluorouracil, adriamycin, cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide) did confer a modest but statistically significant five-year and 10-year OS gain of up to 3% and 4%, respectively over CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy.[4] The observation retrospectively consolidated the status of anthracycline-based chemotherapy regimens as the standard adjuvant chemotherapy in breast cancers of all risks in the 1980's and early 1990's. In an attempt to improve the generally poor outcome of patients with four or more positive lymph nodes, the Milan group explored the new concepts of sequential or alternating adriamycin and CMF (A-CMF) therapy. A total of 359 patients who had four or more positive axillary lymph nodes were randomised to either the sequential chemotherapy of four 3-weekly cycles of adriamycin followed by eight 3-weekly cycles of intravenous CMF for a total of 12 cycles, or to alternating chemotherapy consisting of two cycles of 3-weekly CMF followed by one cycle of 3-weekly adriamycin (repeated thrice for a total of 12 cycles).[5] Although there were slightly more patients in the alternating arm with more than 10 lymph nodes (37% vs 31%), the difference was not statistically significant. Both the relapse-free survival (RFS) and OS were found to be statistically better for patients treated with sequential A-CMF. In the subgroup analysis of patients categorised by the number of positive axillary lymph nodes, the sequential A-CMF approach conferred RFS benefit in patients with four to 10 positive lymph nodes (which constituted 66% of all patients). Their five-year RFS was 67%, whereas those with >10 positive lymph nodes had a 50% five-year RFS. Though this difference was not statistically significant, this was probably due to lack of statistical power and other reasons (Table 1[5]). Due to the manageable tolerance and the encouraging results in high-risk patients, our institution adopted this first-generation sequential Milan regimen as the standard adjuvant chemotherapy in high-risk patients, since the late 1990's till the early years of the next decade.

Recent results further confirmed that the efficacy of this first-generation regimen has stood the test of time. Indeed, a variant of the Milan regimen, the sequential epirubicin-CMF (E-CMF) regimen, has also become popular in Europe and the UK. The UK NEAT/BR9601 study showed superior results in five-year RFS and OS following four cycles of epirubicin followed sequentially by four cycles of CMF (4E-4CMF) as compared to six to eight cycles of CMF.[6] This E-CMF

Table 1. Outcome of the Milan study.[5]

	Sequential A-CMF	Alternating CMF-A	p Value
5-Year relapse-free survival			
All patients	61%	38%	0.001
LN = 4-10	67%	46%	0.005
LN >10	50%	24%	0.16
5-Year overall survival			
All patients	78%	62%	0.005
LN = 4-10	82%	64%	Not significant
LN >10	69%	58%	Not significant

Abbreviations: A-CMF = 4 cycles of adriamycin followed by 8 cycles of CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy; CMF-A = 2 cycles of CMF followed by 1 cycle of adriamycin chemotherapy, repeated for a total of 12 cycles; LN = lymph node number.

Table 2. Outcome of the FASG 05 study.[8]

	FEC50	FEC100	p Value
5-Year disease-free survival			
All patients	54.8%	66.3%	0.03
LN = 1-3	77.6%	71.0%	0.42
LN ≥4	49.6%	65.3%	0.005
5-Year overall survival			
all patients	65.3%	77.4%	0.007
LN = 1-3	83.8%	78.2%	0.63
LN ≥4	60.9%	77.2%	0.001

Abbreviations: FEC50 = chemotherapy of FEC (5-fluorouracil, epirubicin, cyclophosphamide) with epirubicin at 50 mg/m^2; FEC100 = chemotherapy of FEC with epirubicin at 100 mg/m^2; LN = lymph node number.

regimen even compared favourably with some of the taxane-containing regimens in the UK TACT study that was reported in 2009. In the latter, 4162 node-positive or -negative patients (36% had ≥4 positive lymph nodes) were randomised to either 4E-4CMF or 6 cycles of FEC60 (epirubicin at 60 mg/m^2) [the 2 control arms], or four cycles of FEC60 followed by four cycles of docetaxel (the experimental arm).[7] There was no statistically significant difference in outcomes between the different arms. Only in the subgroup of node-positive patients who had HR-negative and HER2-positive cancers has the disease-free survival (DFS) improved after the taxane-containing regimen.

SECOND-GENERATION CHEMOTHERAPY

In 1990, the French Adjuvant Study Group initiated the FASG 05 study in which 565 node-positive patients were randomised to either the French standard of six cycles of FEC50 (epirubicin at 50 mg/m^2) or six cycles of high-dose FEC100 (epirubicin at 100 mg/m^2).[8] The results were published in 2001 after a median follow-up period of 67 months. Both DFS and OS were statistically better in patients receiving six cycles of FEC100, who had a five-year DFS of 67% and a five-year OS of 77%; the respective hazard ratios were 0.73 and 0.65, both of which favoured the FEC100 arm. The subgroup analysis was particularly noteworthy, in that for the FEC50 and FEC100 arms, both the DFS and OS of patients with ≤3 positive lymph nodes yielded no statistically significant difference. Whereas those with >3 positive lymph nodes had significantly better five-year DFS and OS after FEC100 (Table 2[8]). The superiority of the FEC100 arm over the FEC50 arm was maintained at 10 years, with a statistically significant absolute difference of 5.4% and 4.3% for DFS and OS, respectively.[9] Apart from a significantly higher frequency of grades 3 or 4 neutropenia and sepsis without primary prophylactic growth factor support, conceivably there was also more high-grade nausea or vomiting due to the higher dose of anthracycline used. At 10 years, three of 268 patients in the FEC100 arm and one of the 273 patients in the FEC50 arm developed congestive heart failure, and there was only a single case of acute myeloid leukaemia in the FEC100 arm. Interestingly, giving the six cycles of FEC60 (epirubicin at 60 mg/m^2) in a dose-dense fashion (once every 2 weeks) did not improve the outcome at all when compared with the three-weekly FEC60 in the Italian randomised study of more than 1200 women, perhaps highlighting the importance of the total dose rather than the dose density of epirubicin in adjuvant anthracycline-based chemotherapy for breast cancer.[10]

Other taxane-containing second-generation chemotherapy regimens were also tested against the first-generation anthracycline-based regimen of AC (adriamycin, cyclophosphamide), with results published in early 2000's. Both the CALGB 9344 and the NSABP B-28 studies employed four additional sequential cycles of paclitaxel (at 175 mg/m^2 and 225 mg/m^2, respectively) after four cycles of standard AC for node-positive patients.[11,12] Tamoxifen was prescribed concomitantly with chemotherapy in HR-positive patients in the B-28 study rather than sequentially in the CALGB 9344 study. Although both studies demonstrated significantly better DFS for the sequential paclitaxel arm, the NSABP B-28 study failed to confirm the OS benefit conferred in the sequential paclitaxel arm of the CALGB 9344 study.[12] Moreover, in an

exploratory subgroup analysis of the CALGB 9344 study, patients with HR-positive cancers did not benefit from the four additional cycles of paclitaxel. Later updates with refined pathological data confirmed that patients with HR-positive and HER2-negative cancers did not benefit from additional paclitaxel.[13] Patients with four or more positive lymph nodes constituted 54% of all the patients in the CALGB 9344 study and 30% in the NSABP B-28 study, but subgroup analyses of high-risk groups were not conducted in either of the studies.

The US Oncology Group replaced adriamycin in the AC regimen with docetaxel to form the TC regimen, which showed significant improvement in both five-year DFS and OS in a group of patients with relatively early stage breast cancer; just more than half had node-positive disease and only 12% had four or more positive lymph nodes.[14] The seven-year results were still holding up for TC, as the OS was 87% for the TC arm vs 82% for the AC arm with a hazard ratio of 0.69 ($p = 0.032$).[15] On the other hand, the ECOG 2197 study replaced cyclophosphamide in the AC regimen with docetaxel to come up with the AT regimen. However, the new regimen did not result in better outcomes in a cohort consisting of both node-positive or -negative patients among whom none had four or more positive lymph nodes.[16]

As paclitaxel was a self-financed item in Hong Kong public hospitals, and coupled with the inconsistent OS benefit in the two landmark studies and among the subgroups, we did not jump into prescribing the second-generation taxane-containing regimens for our patients. Indeed, we were inclined to continue FAC for our node-positive patients, and prescribe the first-generation Milan regimen of sequential A-CMF among those high-risk patients with four or more positive lymph nodes, as it did not entail extra costs for patients and was relatively inexpensive for the department's budget. Although we were fully aware of the potential benefits of the second-generation FEC100 for high-risk patients, we struggled not to prescribe the regimen, as epirubicin was significantly more expensive for the department and the charging mechanism in the Hospital Authority did not allow us to charge patients extra for epirubicin.

Following publication of the CALGB 9344 study, as well as presentation of the preliminary results of NSABP B-28 study and the updated 10-year results of the FASG 05 study in 2003, we conceived the idea of comparing the promising second-generation regimen of FEC100 with our standard Milan regimen in high-risk node-positive patients at our institution. No toxicity and outcome data have ever been published in Chinese patients treated with the two regimens in this particular patient cohort. After funding was secured for purchasing epirubicin, a randomised phase II study was initiated in mid-2004 with a view to figuring out which one was the better standard to compare with the second- or third-generation taxane-containing regimens. This study recruited its first patient in July 2004 and a total of 43 patients with four or more positive lymph nodes were recruited up to February 2007, at which time the study was prematurely terminated due to slow accrual and other issues. The number of patients recruited at early closure fell short of the study target of 88 patients planned for the study.

THIRD-GENERATION CHEMOTHERAPY

A major reason for the slow accrual of patients in the latter part of the study period was the sequential publication of the results of several randomised studies on third-generation regimens containing the second taxane of docetaxel. The details of the various randomised studies on both second- and third-generation chemotherapy regimens are summarised in Table 3.[3,6,7,11-13,17-27] The patterns of evolution of the various second- and third-generation chemotherapy regimens are also illustrated in the Figure.

Two of the third-generation regimens pivotal in establishing the role of docetaxel are described here. The BCIRG 001 study randomised almost 1500 node-positive patients to receive either six cycles of standard FAC or six cycles of TAC (with docetaxel replacing fluorouracil).[17] Routine prophylactic antibiotics were prescribed for the patients receiving TAC and secondary growth factor prophylaxis was employed when an episode of febrile neutropenia or infection was encountered. There was a 10-fold increase of the frequency of febrile neutropenia for the TAC patients when compared to the FAC patients (24.7% vs 2.5%), but there was also a significant improvement in outcomes. TAC-treated patients had a five-year DFS of 75% and OS of 87%, which represented a gain of 7% (hazard ratio = 0.70) and 6% (hazard ratio = 0.72), respectively over those treated by FAC. In contrast to the earlier CALGB 9344 study, subgroup analyses on HR-positive vs HR-negative subgroups and HER2-positive vs HER2-negative subgroups showed consistent benefit for TAC. Regrettably, those with four or more lymph

Table 3. Summary of results of some of the randomised studies of adjuvant chemotherapy in breast cancer.[3,6,7,11-13,17-27]

Study	No. of patients	LN status (% with LN >4)	Control arm(s)	Experimental arm(s)	5-Year DFS/RFS/EFS (experimental vs control)	5-Year OS (experimental vs control)	Remarks
NEAT/BR9601,[6] 2006	2391	Positive or negative	6 CMF (NEAT) 8 CMF (BR9601)	4E + 4CMF 4E + 4CMF	4E + 4CMF has superior RFS (76 vs 69%)	4E + 4CMF superior (82 vs 75%)	Both statistically better for experimental arms
CALGB 9344,[11] 2003 (updated in 2006)13	3121	Positive (54%)	4 AC	4AC + 4P 4AC (escalated dose)	DFS superior for 4AC + 4P arm only	Superior for 4AC + 4P arm only	DFS not superior in HR-positive and HER2-negative subgroup
NSABP B-28,[12] 2005	3060	Positive (30%)	4 AC	4AC + 4P	4AC + 4P has superior DFS (76% vs 72%)	Equivalent at 85%	Statistically superior for 4AC + 4P arm in DFS
BCIRG 001,[17] 2005	1491	Positive (38%)	6FAC	6TAC	6TAC superior DFS (75% vs 68%)	6TAC superior (87% vs 81%)	Not significant in subgroup of LN ≥4
PACS01,[18] 2006	2000	Positive	6 FE100C	3FE100C + 3T	3FE100C + 3T superior in DFS (78.3% vs 73.2%)	3FE100C + 3T superior (90.7% vs 86.7%)	Not significant in subgroup of LN ≥4
Geicam 9906,[19] 2008	1248	Positive (38%)	6FEC	4FEC + 8p	Better DFS for 4FEC + 8p (78.5% vs 72.1%)	Equivalent (89.9% vs 87.1%)	Also benefit high-risk subgroup
BIG 2-98,[20] 2008	2887	Positive (46%)	4A + 3CMF 4AC + 3CMF	3A + 3T + 3CMF 4AT + 3CMF	DFS marginally better for T-groups; sequential T > concurrent T	Equivalent	Also benefit high-risk subgroup
ECOG 1199,[21] 2008	5000	Positive or negative (33%)	4 AC + 4P	4AC + 12p 4AC + 12t 4AC + 4T	Better for 12p and 4T	Better for 12p only	Both statistically significant
NCIC MA.21,[23] 2009	2104	Positive or negative	4AC + 4P 6CEF	6*dd* EC + 4P	Better 3-yr RFS for *dd* arm (91% vs 85% of AC+P); but = CEF (91% vs 89.5%)	NA	-
GOIM 9902,[22] 2011	750	Positive	4 E120C	4T + 4E120C	Similar DFS ~73.4%	Similar ~89.5-90.1%	-
TACT,[7] 2009	4162	Positive or negative (36%)	8FE60C or 4E + 4CMF (oral or iv, q4w)	4FE60C + 4T	Equivalent DFS (75.6% vs 74.3%)	Equivalent	DFS better in HR-negative and HER2+ node+ group
CALGB 9741,[26] 2003 (updated in 2006)[13]	1973	Positive (40%)	4AC + 4P 4A + 4P + 4C	*dd* 4AC + 4P *dd* 4A + 4P + 4C	4 yr DFS better for *dd* arms (82% vs 75%)	Hazard ratio 0.69 for *dd* arms	*dd* arms statistically better
AGO,[27] 2010	1284	Positive (100%)	4EC + 4P	*dd* 3E + 3P + 3C	Superior EFS for *dd* arm (70% vs 62%)	Superior OS for *dd* arm (82% vs 77%)	Both statistically significant
NSABP 30,[24] 2010	5351	Positive (33%)	4AT 4TAC (concurrent & shorter arms)	4AC + 4T (sequential & longer arms)	Better 8-yr DFS for 4AC + 4T (74% vs 69%)	Better 8-yr OS for 4AC + 4T (83% vs 79%)	-
BCIRG 005,[25] 2011	3298	Positive (39%)	6TAC	4AC + 4T	Equivalent ~79%	Equivalent ~88-89%	-

Abbreviations: LN = lymph node; DFS = disease-free survival; RFS = relapse-free survival; EFS = event-free survival; OS = overall survival; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; E = epirubicin; AC = adriamycin, cyclophosphamide; P = 3-weekly palcitaxel; HR = hormone receptor; FAC = 5-fluorouracil, adriamycin, cyclophosphamide; TAC = docetaxel, adriamycin, cyclophosphamide; FE100C = 5-fluorouracil, epirubicin at 100 mg/m^2, cyclophosphamide; T = 3-weekly docetaxel; p = weekly paclitaxel; A = adriamycin; t = weekly docetaxel; CEF = cyclophosphamide, epirubicin, 5-fluorouracil; *dd* = dose-dense; EC = epirubicin, cyclophosphamide; NA = not available; E120C = epirubicin at 120 mg/m^2, cyclophosphamide; FE60C = 5-fluorouracil, epirubicin at 60 mg/m^2, cyclophosphamide; iv = intravenous; q4w = once every 4 weeks; HER2 = human epidermal growth factor 2; C = cyclophosphamide; AT = adriamycin, docetaxel; TAC = docetaxel, adriamycin, cyclophosphamide.

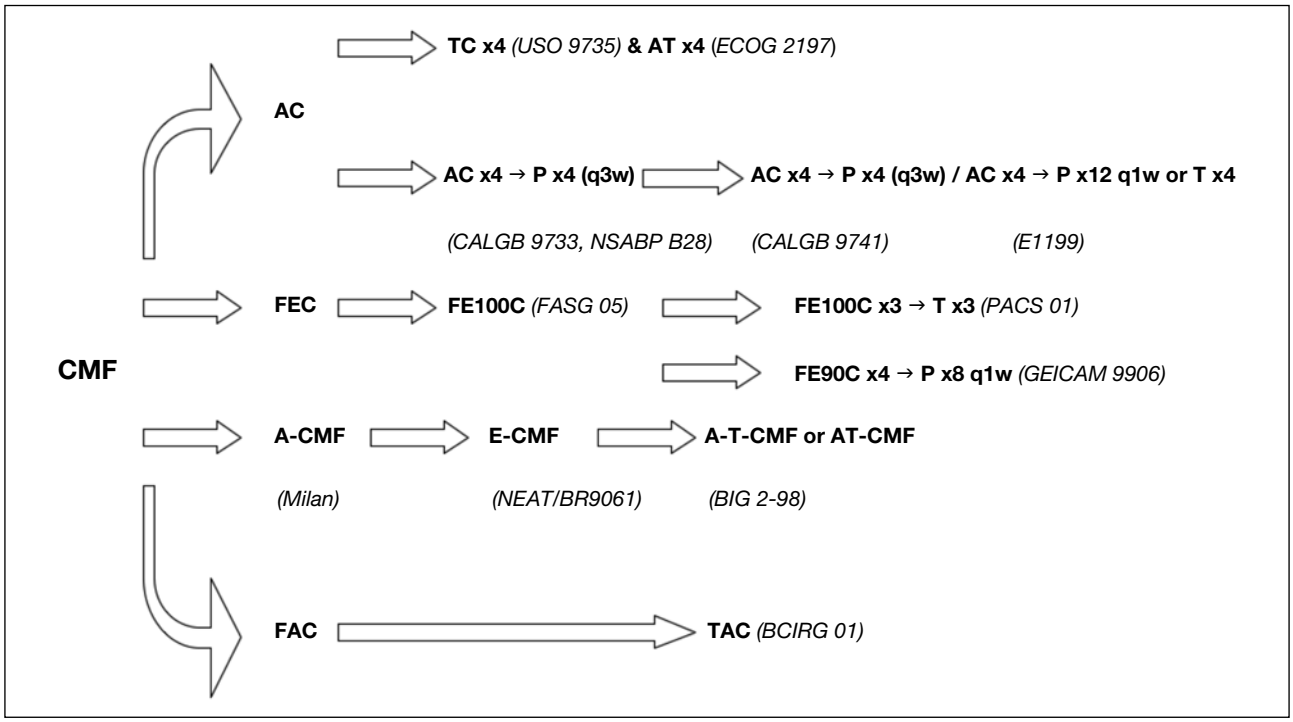

Figure. Evolution pathways of adjuvant chemotherapy regimens from CMF to anthracycline-based chemotherapy and third-generation taxane-based chemotherapy.
Abbreviations: A = adriamycin; AC = adriamycin, cyclophosphamide; AT = adriamycin, docetaxel; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; E = epirubicin; FE100C = 5-fluorouracil, epirubicin at 100 mg/m^2, cyclophosphamide; FE90C = 5-fluorouracil, epirubicin at 90 mg/m^2, cyclophosphamide; FAC = 5-fluorouracil, adriamycin, cyclophosphamide; P = palcitaxel; q1w = once every week; q2w = once every 2 weeks; q3w = once every 3 weeks; T = 3-weekly docetaxel; TAC = docetaxel, adriamycin, cyclophosphamide.

nodes (which constituted about 38% of all patients) did not benefit in a statistically significant manner from TAC (according to subgroup analysis), in contrast to those with one to three positive lymph nodes. Later analysis in a retrospective fashion showed that the DFS benefit of TAC was mainly in patients with the luminal B phenotype; benefits in those with triple negative and HER2 phenotypes were not statistically significant, and those with luminal A phenotype did not benefit at all from TAC.[28]

Another approach of adding docetaxel to anthracycline in a sequential manner was reported in the PACS 01 study in 2006, in which 2000 patients were randomised to either six cycles of FEC100 or three cycles of FEC100 followed by three 3-weekly cycles of docetaxel at 100 mg/m^2; 38% of the patients had four or more positive lymph nodes.[18] The docetaxel-containing regimen was shown to confer a five-year DFS gain of 5% and OS gain of 4% over FEC100. Again, the DFS benefit of the docetaxel-containing regimen in patients with four or more positive lymph nodes was not statistically significant.

On the other hand, two other randomised studies did show advantages for taxane-containing regimens in high-risk node-positive patients.[19,20] The Geicam 9906 study from Spain explored sequential weekly paclitaxel (vs 3-weekly paclitaxel in CALGB 9344 and NSABP B-28 studies) after four cycles of three-weekly FEC90 (epirubicin at 90 mg/m^2, vs 4 cycles of AC in CALGB 9344 and NSABP B-28 studies) in more than 1200 node-positive patients in whom 38% had four or more positive lymph nodes.[19] Eight-weekly cycles of paclitaxel at 100 mg/m^2 were given after four cycles of FEC90, which were compared with six cycles of FEC90. Although the difference in OS was not statistically significant, there was a statistically significant difference in favour of the sequential paclitaxel arm for DFS and distant RFS. Patients with four or more positive lymph nodes were shown to have statistically significant better DFS when treated with sequential paclitaxel.

The BIG 02-98 study randomised 2887 node-positive patients into four arms.[20] The two control arms represented two popular European standards in

the late 1990's for node-positive disease. They were the sequential A-CMF (4 cycles → 3 cycles) and the sequential AC-CMF (4 cycles → 3 cycles) regimens, both being variants of the original Milan regimen discussed earlier. Docetaxel was added sequentially after adriamycin but before CMF in the A-CMF regimen (A-T-CMF, 3 cycles → 3 cycles → 3 cycles) as one of the two experimental arms, and docetaxel replaced cyclophosphamide in the sequential AC-CMF regimen to become the AT-CMF regimen (4 cycles → 3 cycles) as the second experimental arm. The arm with the triple sequence of A-T-CMF emerged as the regimen that produced the best DFS, the difference from the control arms being statistically significant. The DFS benefit was mostly in patient subgroups with HR-negative disease and those with four or more positive lymph nodes. The five-year DFS was 69% after A-T-CMF, which was significantly superior than the 61% noted for A-CMF in the subgroup with four or more positive lymph nodes.

With no apparent improvement in outcome conferred by the second-generation and inconsistent benefit even by some of the third-generation taxane-containing regimens in high-risk node-positive patients, statisticians quickly used the published data for meta-analyses. One of the literature-based meta-analyses published in 2008 included more than 12,000 women from 13 randomised studies.[29] It showed taxane-containing regimens conferred an absolute five-year DFS gain of 5% and OS gain of 3%, reminiscent of the magnitude of benefit obtained by anthracycline-containing regimens over CMF (demonstrated by the EBCTCG in earlier meta-analyses). Among the various other analyses which were not the focus of this paper, the authors pooled all the four randomised studies alluded to in previous discussions in which subgroup analysis was performed with respect to the number of positive lymph nodes, which included: BCIRG 001, PACS 01, Geicam 9906, and BIG 02-98. In this cohort of more than 2400 patients, there was a statistically significant benefit in five-year DFS in favour of taxane-treated patients, with a hazard ratio of 0.74.

RE-ENGINEERING OF CHEMOTHERAPY REGIMENS IN THE POST-TAXANE ERA

Perhaps the ECOG 1199 study reported in 2008 has elucidated the importance of the administration schedule of taxanes to optimise treatment outcomes.[21] A total of 4950 patients were recruited and randomised to four different schedules of sequential taxane administration after four cycles of AC, namely three-weekly paclitaxel, weekly paclitaxel, weekly docetaxel, or three-weekly docetaxel. In short, only those treated with the weekly paclitaxel schedule were observed to have improved DFS and OS over the very popular three-weekly schedule; the three-weekly docetaxel schedule was also shown to have statistically superior DFS but not OS. Among the almost 5000 patients recruited, slightly less than 12% were node-negative and 33% had four or more positive lymph nodes. All the patients, irrespective of the HR and HER2 status, treated with weekly paclitaxel appeared to benefit, which differed from the findings of subgroup analysis in the CALGB 9344 study using three-weekly paclitaxel. However, there was no subgroup analysis addressing the high-risk group in this study. Future studies on node-positive breast cancer patients, including those at high risk with four or more lymph nodes, should employ one of the more optimally dosed and scheduled taxane-containing third-generation regimens as the control arm to compare with the more novel approaches and agents.

An example of the lack of superior outcomes in patients treated by taxane-containing regimens which might be attributed to suboptimal scheduling is the MD Anderson study published in 2011. The study randomised 511 node-positive patients to either eight cycles of FAC, or four 3-weekly cycles of paclitaxel followed by four cycles of FAC.[30] No difference in outcomes was observed. Another possible reason was the relatively small size of the study, which lacked statistical power to detect small differences.

Apart from the schedule of taxane administration, the difference in the total dose of anthracycline (epirubicin in particular) used in the control and experimental arms may have played a role in influencing the difference in outcomes between the treatment arms. The Italian GOIM 9902 study randomised 750 node-positive patients to receive four cycles of high-dose EC (epirubicin at 120 mg/m^2) or four cycles of 3-weekly docetaxel followed by four cycles of high-dose EC.[22] Despite longer treatment durations with twice as many cycles of chemotherapy and the addition of upfront docetaxel, there was no difference in DFS and OS between the two arms. Similarly, in the NCIC MA 21 study, six cycles of the non–taxane-containing regimen of high-dose CEF (epirubicin at 120 mg/m^2) was superior to eight cycles of the CALGB 9344 AC-P sequential regimen in RFS at five years. The other experimental arm of six cycles of dose-dense EC

(epirubicin at 120 mg/m^2, once every 2 weeks) followed by four cycles of three-weekly paclitaxel did not outperform six cycles of CEF that did not contain any taxane.[23] Overall, there is robust evidence to support high-dose anthracycline and in particular epirubicin. Together with taxane, it may still be the other key component of the axial skeleton, upon which novel agents can build to improve patient outcome.

There are several recently published studies that may have shed more light on the choice of optimal chemotherapy regimens in node-positive (if not confined to only high-risk node-positive patients). Now that third-generation taxane-containing chemotherapy regimens have gradually established their supremacy over other regimens of the past, we oncologists would very much like to know which one in this armamentarium is the hottest pick. Both the NSABP B-30 study and the BCIRG 005 study examined the sequential anthracycline-taxane approach against the concurrent approach; 33% and 39% of the randomised patients in the respective studies had four or more positive lymph nodes.[24,25]

In the former study reported in 2010, 5351 node-positive women were randomised to four cycles of adriamycin plus docetaxel (AT), four cycles of TAC, or four cycles of AC followed by four cycles of docetaxel.[24] The treatment with sequential anthracycline and docetaxel, which was also longer in duration consisted of eight instead of four cycles, attained statistically superior DFS and OS compared to AT. Four TAC was also better for DFS but not OS when compared with AT. On the other hand, the BCIRG 005 study included only node-positive patients who were also HER2-negative.[25] Six cycles of TAC (concurrent anthracycline-taxane) was compared with four cycles of AC followed by four cycles of docetaxel (sequential anthracycline and taxane) in 3298 patients. In this more equal comparison (6 vs 8 cycles) of the anthracycline-taxane partnership, there was absolutely no difference in five-year DFS or OS, which suggested that both sequential and concurrent approaches in node-positive patients are equally effective. The results of the NSABP B-38 study which compared six TAC with either dose-dense AC-P for a total of eight cycles (once every 2 weeks) or dose-dense AC-PG (paclitaxel + gemcitabine) for a total of eight cycles (once every 2 weeks) are eagerly awaited. Their findings may determine the optimal regimens of adjuvant chemotherapy for patients with node-positive (and high-risk node-positive) breast cancer.

A LOOK INTO THE FUTURE

In the first analysis of our institution's randomised phase 2 study that closed early, the outcome of patients with four to nine positive lymph nodes treated by the earlier-generation chemotherapy regimens did not fare as badly as expected. However, those with 10 or more lymph nodes did extremely poorly, especially after the first-generation regimen of sequential A-CMF chemotherapy (unpublished data). Another contemporary cohort of patients treated in the same institution in the latter part of the study period (2006-2007) with third-generation taxane-containing regimens of TAC, and sequential FEC100 and docetaxel (PACS 01 regimen) was also retrospectively reviewed. With a shorter median follow-up period, they did not appear to outperform results of earlier-generation regimens by a statistically significant margin (unpublished data). These results are not too unexpected due to the small number of the patients both in the study and in the contemporary cohort, and the non-apparent benefits of some third-generation chemotherapy regimens in subgroups of high-risk node-positive patients mentioned earlier.

The unsatisfactory outcome of the high-risk patients, particular those with 10 or more lymph nodes, certainly calls for more innovative approaches. The CALGB 9741 study reported in 2003 already experimented the dose-dense approach of delivering sequential taxane after AC.[26] A total of 1973 node-positive patients, among whom 40% had four or more positive lymph nodes, were recruited for randomisation to two control arms and two experimental arms. The two control arms consisted either of four cycles of AC followed sequentially by four cycles of paclitaxel for a total of eight cycles (AC-P) delivered once every three weeks, or four cycles each of the single drugs of adriamycin, paclitaxel and cyclophosphamide (A-P-C) sequentially for 12 cycles delivered once every three weeks. In the experimental arms, patients were treated with either the AC-P sequence or the triple sequence A-P-C in a dose-dense manner with each cycle given once every two weeks with growth factor support. The dose-dense arms had statistically superior DFS and OS at five years, but as in the CALGB 9344 study that also employed the sequential AC-P approach, subgroup analysis did not show survival benefits in HR-positive patients (Table 3).

The recent report of the German study by the AGO group employing a dose-dense delivery of escalated doses of anthracycline, taxane and cyclophosphamide, however, showed more encouraging results.[27] The

study recruited 1284 patients with four or more positive lymph nodes who were randomised to: (1) four cycles of the standard three-weekly EC (epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2), followed by four 3-weekly cycles of paclitaxel at 175 mg/m^2, or to (2) the experimental intense dose-dense (IDD) approach consisting of three cycles of sequential epirubicin (150 mg/m^2) once every 2 weeks, followed by three cycles of paclitaxel (225 mg/m^2) once every 2 weeks, and then three cycles of cyclophosphamide (2.5 g/m^2) once every 2 weeks. Apart from the completion of nine cycles of chemotherapy within 18 weeks in a dose-dense manner, the total doses of epirubicin and cyclophosphamide (though not the paclitaxel) in the IDD arm were increased by approximately 25% and >300%, respectively. The 70% five-year event-free survival (EFS) and 82% five-year OS of the IDD arm were impressive, compared to the corresponding 62% and 77% of the control arm; both differences being statistically significant (Table 3). Moreover, the subgroup of patients with 10 or more positive lymph nodes carried an EFS of 63% at five years, which was substantially better than that of the control group at 51%. The numerical superiority of the IDD arm in the subgroup with four to nine positive lymph nodes was marginal at a p value of 0.099, but the five-year EFS at 76% was still respectably higher than that of the control arm at 70%.

CONCLUSION

This report summarised the results of all pertinent randomised studies reported in literature that explored the relative merits of various generations of adjuvant chemotherapy used in high-risk node-positive breast cancer patients. The relevant experience of the author's institution in this cohort of patients was also briefly described. State-of-the-art taxane- and anthracycline-containing regimens are generally preferred to produce more favourable results. In view of the generally poor outlook of this cohort of patients, new drugs with different mechanisms of cell kill and / or synergism with the current drugs, as well as the approach of combining dose-dense delivery in conjunction with dose escalation of the existing active drugs, should be further explored in devising novel strategies of adjuvant chemotherapy.

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