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Quantum Leaps in Treatment of High-risk Breast Cancer? Prove it!

Vicky E. Jones and Derek Raghavan

THE TREATMENT of breast cancer has been the focus of intense study over the past few decades, and adjuvant trials have been conducted for more than 20 years. The benefit of adjuvant chemotherapy is established in node-positive breast cancer, with an overall reduction of 28% in the annual hazard rate for a relapse and a 16% reduction in the annual hazard rate for mortality [1]. The absolute benefit is defined by the actual risk to the patient. There is, however, controversy regarding the relative merits of disease-free (DFS) and overall survival (OS) as the best index of outcome. Similarly, the apparent impact of treatment decreases if one cites the *actual* vs. percentage reduction in relapse rate or death [2]. Endeavours to create a reliable method to predict an individual patient's risk of relapse continue, complicated by a burgeoning list of prognostic factors. Valid questions remain as to whether subgroups can be defined that have either such a good prognosis that conventional adjuvant therapy is not warranted, or are at sufficiently high risk for recurrence that other adjuvant strategies should be entertained.

A group of patients whose management has not been adequately addressed in the published literature is those with 10 or more positive lymph nodes.

The natural history of breast cancer is heterogeneous. Each stage grouping includes patients with naturally indolent disease as well as those destined to relapse early. Prognostic factors have been defined in an attempt to delineate risk profiles, potentially allowing more individual tailoring of adjuvant treatment and a clearer definition of the aims of therapy.

Available prognostic factors can be divided into two broad categories: (i) standard histopathological factors and (ii) newer biochemical or molecular indices. The former includes tumour size, nodal status, histological and nuclear grade, receptor status and vascular/lymphatic invasion. Of this group, the most dominant known factor is the degree of nodal involvement, reflecting overall tumour burden and metastatic potential. The relapse rate is a continuum predicated on increasing nodal involvement [3, 4]. Based on 5-year DFS data from the National Surgical Adjuvant Breast and Bowel Project (NSABP), trials B04 and B05, several broad categories of nodal involvement have been described: 0 (85% 5-year DFS), 1–3 (63%), 4–6 (41.9%), 7–12 (27.7%) and ≥ 13 (16.4%) [5]. In general, patients with ≥ 10 nodes involved are grouped together as having a uniformly poor prognosis (5-year DFS, 11–27%) [6, 7]. Whether this is a function of the innate biology (aggression) of these tumours or whether it is due to advanced chronology of the disease remains the subject of controversy [8]. Tumour size is an independent predictor of tumour burden and metastatic potential in both node-negative and node-positive breast cancer [9, 10]. As the number of nodes involved increases, however, the significance of size diminishes, such that those with ≥ 4 nodes have a poor survival regardless of tumour size [9, 10]. Positive steroid receptor status conveys a modest (8%) reduction in relapse and increase in survival irrespective of nodal status or tumour size [11–13]. In postmenopausal women, with increasing nodal involvement, the outcome difference reflected by receptor status becomes negligible [4]. Histological and nuclear grades are independent prognostic variables, significantly influencing DFS and OS in node-negative as well as node-positive patients [9, 14]. In patients with ≥ four involved nodes, the 5-year DFS for histological grade 1 tumours was 56%, grade 2 was 37%, and 25% for grade 3 [15].

A listing of newer prognostic factors includes DNA content, proliferation indices, cathepsins, oncogenes, growth factors/growth factor receptor expression, and tumour suppressor genes [16]. The S-phase fraction has been reported to discriminate between high and low risk for relapse but generally correlates with receptor and nodal status, and size [17, 18], and may be of more value in the node-negative patient. Cathepsin D overexpression is more frequent in aneuploid tumours and in such tumours predicts for a high rate of recurrence [19]. HER2/*neu* amplification in node-positive patients predicts for shorter DFS and OS, independent of other factors [20, 21]. While these may ultimately prove to be valuable in discriminating subsets of patients with low or high risk, they have not yet been rigorously evaluated prospectively. Differences in laboratory technique, quantification and reproducibility remain problems for their routine clinical use. In addition, multivariate analysis correlating their prognostic significance in the context of established prognostic determinants must also be completed. It has already been shown, for example, that HER2/*neu* expression in node-positive patients imparts a poorer prognosis, but that this effect is lost when > 10 nodes are involved [22].

For the purpose of investigating alternative adjuvant strategies focused on high-risk patients, a reasonably uniform population of patients with similar prognosis is necessary. Given our current understanding of prognostic factors, the group of patients without clinically obvious visceral metastases who have the poorest prognosis appears to be those with ≥ 10 lymph nodes involved.

The so-called "natural history" data bases [3, 6] demonstrate the poor DFS and OS of patients with ≥ 10 nodes who received local treatment only. At 5 years, the DFS was 26–28% and the OS was 27–44%, while at 10 years the DFS was 15% and the OS was 24%. Table 1 compares natural history data to results from several major adjuvant trials whose published reports included data for the ≥ 10 node subset. It should be noted that many trials report their results using N1–3 and N ≥ 4 subsets, not separately evaluating the ≥ 10 node group [23–25], thus reducing the clarity of prognostic implication of this group.

The results of the first Milan cyclophosphamide/methotrexate/5-fluorouracil (CMF) adjuvant trial, (control vs. adjuvant CMF × 12 months) confirmed the influence of the number of axillary nodes on the prognosis of the patients [26]. The median duration of DFS and OS was improved by administration of adjuvant CMF in all nodal subgroups, most particularly in the group with one to three nodes involved. The ≥ 10 node-positive subgroup had a median DFS of 9 months (control) vs. 39 months (CMF) and median OS of 31 months vs. 81 months. The subsequent Milan CMF trial (comparing 6 vs. 12 months adjuvant CMF) confirmed the benefit seen in the original study, but with no advantage conferred by prolonged treatment. Despite adjuvant treatment, the ≥ 10 node subset had a 5-year DFS of only 35%, with 5-year OS of 60% [27].

Investigators at the MD Anderson Hospital, Houston, Texas conducted a series of adjuvant studies between 1974 and 1986 using doxorubicin-based regimens which included patients with ≥ 10 nodes [28–30]. Combined results from four sequential trials with a median follow-up of 92 months reveal a 5-year DFS of 41% and a 5-year OS of 57%. The utility of these data are limited by the non-comparative nature and the long interval of accrual, with different periods of median follow-up and different staging approaches. Although there was no significant difference in DFS and OS between trials, in the earlier trials 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) was followed by CMF for a total treatment duration of 2 years. When a comparison was made of different trials of adjuvant chemotherapy [30], only the FAC–CMF combination had a significant improvement in DFS in the ≥ 10 node subgroup. Once again, stage shift may be a confounding factor, as outlined below. The DFS from each of the other trials [using doxorubicin/cyclophosphamide/prednisone (AC), CMF, and CMF/vincristine/prednisone (CMFVP) regimens] were not significantly different from the natural history data base. Thus, standard doxorubicin regimens have not been shown to have superior results as compared with non-doxorubicin regimens in these patients.

Dose intensification has been an attractive potential strategy since Hryniuk's report concerning dose intensity in metastatic breast cancer [31]. Retrospective evaluations suggested better outcomes with increasing dose intensity [31–33]. However, there

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Table 1. DFS and OS results in ≥ 10 nodes positive

Group	No. of patients	Median F/U (months)	DFS			OS		
			3 years	5 years	10 years	3 years	5 years	10 years
Moon [6]‡	119	61	42	28	15	65	44	24
Nemoto [3]‡	1088	60	NA	26	NA	NA	27	NA
Milan (CMF) [27]	71	96	50	35	NA	NA	60	NA
MDA (FAC) [29]	284	92	55	43	31	76	57	38
Milan [58]:								
Doxorubicin/CMF	55	72	54	47	NA	NA	59	NA
CMF/doxorubicin	67	72	50	31	NA	NA	48	NA
Johns Hopkins [46]	62	40	53*	NA	NA	81*	NA	NA
Duke (BMT)†	85	38	72	NA	NA	NA	NA	NA
Milan (BMT) [53]	48	21	93	NA	NA	NA	NA	NA
Tajima (BMT) [52]	18	41	66	56	NA	NA	65	NA

*DFS/OS at 40 months.
†Dr J. Vredenburgh, Duke University.
‡Natural history data base.

are few prospective *randomised* trials studying dose intensity. Tannock *et al.* [34] reported conventional dose CMF to be superior to a lower dose CMF, whereas a comparison of high-dose FAC vs. standard FAC at MD Anderson Hospital failed to support an advantage for dose intensity [35]. The latter study was subsequently shown to have no significant difference between arms in the dose actually delivered to the patient [36]. The inability to deliver significantly different dose intensities within the range of conventional chemotherapy may limit the effectiveness of this approach [37], but it should be noted that the previous studies were conducted in metastatic disease, which may not reflect the adjuvant situation.

Ongoing trials are evaluating dose intensity in the adjuvant setting for node-positive breast cancer. NSABP study B22 compares three schedules of AC: standard AC vs. AC with intensified C at same cumulative dose vs. AC with intensified and higher cumulative dose of cyclophosphamide [38]. A recently completed Cancer and Leukemia Group B (CALGB) trial compared three schedules of C, A and F (CAF): standard CAF × 6, intensified CAF × 4, and low dose CAF × 4 [39]. Preliminary results from the latter study suggest that patients in the low dose arm fared worse as compared with the other two arms, but longer follow-up will be needed to discern whether there is an advantage to the higher intensity arm and whether the initial difference is sustained.

An unrandomised pilot study conducted at Johns Hopkins evaluated dose intensity in the high risk ≥ 10 node population using a 16-week regimen of C, A, F, V and M with leucovorin. At early follow-up (median 17 months), the actuarial 3-year DFS was projected to be 80%. However, with longer follow-up, more relapses have been seen and at a median follow-up of 40 months, the DFS has decreased to 53% [40, 41]. Of note, in patients with ER-negative tumours, a DFS of 73% was seen at 40 months, suggesting heterogeneity of response even within the high risk group. In the ≥ 10 node high risk group, dose intensity within the limits of conventional chemotherapy may not be able to confer a distinct treatment advantage, although the use of growth factors may now allow more dose intensive studies to be conducted.

There are several facets to the problem of tumour cell heterogeneity: intrinsic biochemical drug resistance, emergence of resistance during treatment and kinetic heterogeneity, i.e. differences in growth rate, growth fraction, and kinetic sensitivity to treatment [42]. The optimal dosing and sequencing of drugs is one strategy for targeting aspects of tumour cell heterogeneity. The Goldie–Coldman approach, based on Skipper's model of exponential tumour growth, predicts that an alternating schedule of treatment will maximise cell kill. However, clinical trials have not supported this approach in advanced breast cancer. Norton has proposed that breast cancer follows a Gompertzian growth model, with an early exponential growth phase leading to a gradual slowing and plateau [43], leading to the concept of scheduling strategies with late intensification by crossover schedules [44]. Buzzoni and colleagues in Milan conducted an adjuvant study for patients with more than three nodes to address the question of optimal drug scheduling [45]. Patients received either alternating CMF/A for a total of 12 cycles or four cycles of A followed by eight courses of CMF. The sequential schedule was significantly superior both in 5-year DFS (61 vs. 38%) and 5-year OS (78 vs. 62%), with the benefit observed in all nodal subsets. The 5-year DFS for the > 10 node group was 50 vs. 24% and the 5-year OS was 69 vs. 58%. In patients with > 10 nodes, unlike those with four to 10 nodes in whom the improved benefit was present throughout, the difference in treatment outcome did not become evident until after the second year. While the strategy of optimal sequencing resulted in overall improvement in this subset, the tumour burden and population of resistant cells is likely to have been so high in many of these patients that early relapses were not affected. Seeking to improve the sequential strategy, Norton and colleagues have conducted a feasibility study with four cycles of A followed by three cycles of dose-intensive C with G-CSF support. The treatment was well tolerated but outcome results are not yet available, although a comparison of this regimen and the previously described A/CMF sequence is in progress [46].

High-dose chemotherapy with autologous stem cell support has been investigated in treatment of advanced breast cancer for the past decade although much of the available information is characterised more by rhetoric than quantifiable, comparative data. The regimens used and the patients treated have evolved over the years, from the pilot studies with single-agent chemotherapy in refractory patients to the current approach of high-

dose combination chemotherapy in patients responding to standard chemotherapy. Although certainly not yet proven superior to standard chemotherapy with respect to improved overall survival [47], the total response rate of nearly 90% and the complete remission rate of 60–70% are two to three times greater than that seen with the best conventional therapy [48]. While the median time to relapse ranges from 12 to 21 months and the median survival duration from 20 to 24 months [47, 48], 20–25% of the complete responders (15–20% of the total patients) remain free of progression for prolonged periods (2–4 year follow-up) [48–50]. However, the toxicities are considerable and iatrogenic mortality rates of 5–10% are much higher than with conventional chemotherapy.

The responses seen in advanced breast cancer to treatment with induction chemotherapy followed by high-dose intensification and stem cell support has led to similar approaches now being investigated in the adjuvant setting for high-risk patients, in whom presumably the tumour burden and resistant cell population would be lower. Peters and colleagues from Duke University enrolled 102 women with stage II–III breast cancer and $\geq$ 10 positive nodes, for treatment with four cycles of standard dose CAF followed by high-dose chemotherapy with C, cisplatin, and 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU) with autologous bone marrow support. To date, 85 are treated and evaluable. At a median follow-up of 38 months, disease-free survival is 72% with no relapses reportedly having occurred after 28 months, ([51] Dr. Vredenburgh, Duke University). The CALGB is now conducting a phase III randomised trial based on these results, in which patients are treated with four cycles of standard dose CAF followed by randomisation to standard dose C/cisplatin/BCNU vs. high-dose C/cisplatin/BCNU with marrow support. Tajima *et al.* reported results of high-dose adjuvant chemotherapy with bone marrow support in 18 patients with $\geq$ 10 nodes involved. At a median follow-up of 41 months, 67% remained disease free [52]. Gianni *et al.* from Milan treated a heavily selected group of 48 patients with $\geq$ 10 lymph nodes involved with high-dose sequential chemotherapy (with dose-intense alkylating agents and methotrexate) and bone marrow support [53]. With a median follow-up of 21 months, disease-free survival was 93%, compared with 43% for concomitant but non-randomised controls receiving sequential A-CMF. Encouraged by these results, consideration is being given to a prospective randomised trial comparing this high-dose adjuvant regimen to their conventional sequential A-CMF regimen. In Intergroup study 0121 conducted by ECOG/SWOG, patients with $\geq$ 10 nodes are treated with six cycles of standard CAF followed by randomisation to observation vs. high-dose cyclophosphamide/-thiotepa with marrow support. The results to date from the high dose chemotherapy/marrow support adjuvant studies are certainly of interest but it must be emphasized are preliminary in nature and represent heavily biased comparisons predicated on patient selection and trial design. The ongoing CALGB 9082 and Intergroup 0121 phase III randomised studies of high dose vs. standard chemotherapy will be important in defining the role of dose intensification in this patient population. This applies to this group of patients in particular because of the phenomenon of stage migration [54]. During the evolution of such schedules, staging methodology has changed, with the introduction of computed tomography (CT) scanning, magnetic resonance imaging (MRI) scanning of bone marrow and also improved methodology for the assessment of marrow infiltration with monoclonal antibodies [55]. Furthermore, in the workup for bone marrow transplant, marrow biopsy is a routine test that usually was not included in standard protocols of staging for this disease in the past. Finally, there are often delays of several months during the induction phase of treatment prior to transplant, thus imposing another selection bias and precluding a rational comparison with historical controls.

What role does radiation play in treatment of these patients? Fowble *et al.* analysed risk factors for isolated local–regional recurrence following mastectomy and found a correlation with number of involved nodes ($\geq$ four nodes) and tumour size ($\geq$ 5 cm), with a 15% local recurrence rate despite adjuvant chemotherapy [56]. In the first 8 patients on the Duke pilot study, 3 had isolated local relapses. All subsequent patients (n = 77) have been treated with locoregional radiation and no further local relapses have occurred. Transplant mythology now would have all such patients receiving radiotherapy to sites of previous bulky disease. Although radiation for reduction of local relapse may be a means of prolonging DFS, it is not likely to impact on overall survival in these patients, as their risk of distant relapse is so high.

Endocrine treatment in this high-risk subset has not been specifically investigated, although prolonged administration of tamoxifen in receptor-positive patients following chemotherapy is incorporated into the CALGB and Intergroup studies discussed previously. CMFP with or without oophorectomy was studied by the International Breast Cancer Study Group in premenopausal patients between 1978 and 1981. Results in patients with > 10 nodes involved supported improved disease-free survival and overall survival in the chemo-oophorectomy arm, although this did not become apparent until after 4 years of follow-up. Late relapses, in particular skeletal metastases, were reduced by addition of oophorectomy [57].

Data arising from recent trials of new drugs for the treatment of breast cancer are fairly limited, with taxol and its derivatives presently receiving the most emphasis. Taxol has now been fairly extensively studied in metastatic breast cancer with promising preliminary response rates. Investigations with other new drugs such as CPT11, carboplatin and topotecan are underway in metastatic breast cancer. Adjuvant studies in this patient population with new agents remain to be done.

In conclusion, a subset of patients with an exceptionally high risk for relapse of breast cancer can be defined on the basis of $\geq$ 10 nodes involved by tumour at presentation, although the precision of such prognostication will require further refinement. Standard dose adjuvant chemotherapy offers improved DFS and OS compared with historical and randomised controls treated with local manoeuvres alone, but their outcome remains poor despite the systemic therapy. High-dose chemotherapy with marrow support and the innovative schedules of delivery have shown a surprisingly high preliminary response rate, the impact of which may have been blown out of proportion. It is of critical importance that well-structured, randomised trials be completed, comparing high-dose or schedule-dependent strategies to standard regimens, before the community is required to sustain the cost of such innovation as "routine" treatment. Of particular interest will be those studies that have a uniform approach to staging before randomisation and which analyse outcomes on the basis of intention to treat. In a population of patients with so much to lose, it is of particular importance that we avoid the design errors from past studies and that we subject innovative strategies of management to stringent and critical evaluation of outcome. We are under pressure from the community to "deliver". However, deviation from scientific method will not speed our progress.

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