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Systemic Treatment for Locally Advanced Breast Cancer: What we Still Need to Learn after a Decade of Multimodality Clinical Trials

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Multimodality therapy of locally advanced breast cancer with initial chemo-(hormono)-therapy followed by locoregional treatment has become increasingly popular during the past decade. A paucity of large randomised clinical trials leaves the following unanswered questions: does systemic treatment impact on long-term control of distant metastases? What is the best treatment sequence? The most effective drug combination? The optimum treatment duration? Future prospects in the treatment of locally advanced breast cancer include the use of haematopoietic growth factors to increase the dose-intensity of neoadjuvant chemotherapy, the investigation of autologous bone marrow transplantation with high dose chemotherapy on a larger scale, the development of new approaches designed at interrupting the "autocrine loop" of breast cancer local growth factors and the introduction of diphosphonates in the adjuvant systemic therapy.
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INTRODUCTION

IN WESTERN countries, locally advanced breast cancer (LABC) represents an infrequent but fascinating subgroup of primary breast cancers, the incidence of which is in the range of 10–30% [1]. For this very heterogeneous group of patients (to which belongs a relatively indolent T3N0M0 tumour but also an aggressive inflammatory carcinoma involving the entire breast), the medical oncology community has witnessed a growing number of multimodality clinical trials, with the incorporation of systemic chemo- and hormonal therapy. This review will try to address the most important issues which pertain to the systemic treatment for LABC, namely: why should one give systemic therapy? when? for how long? and how aggressively?

The primary focus will be on the small number of controlled clinical trials performed in this area. New and important questions for future randomised clinical trials will also be presented and briefly discussed.

SYSTEMIC TREATMENT FOR LABC: WHY?

Only one large, prospective randomised clinical trial performed by the EORTC has attempted to clarify the contribution of hormonal manipulation, chemotherapy, or a combination of both to the management of LABC with loco-regional radiotherapy [2] (Table 1). In 363 evaluable patients, who all met the criteria of "inoperable breast cancer" according to Haagensen [3], time to first progression was delayed significantly by both endocrine treatment (consisting of ovarian irradiation—prednisolone in premenopausal women and tamoxifen in postmenopausal women) and chemotherapy [consisting of cyclophosphamide, methotrexate and 5-fluorouracil (CMF)]. The greatest effect was achieved by the combination of endocrine treatment and chemotherapy prescribed after completion of radiotherapy to the breast, chest wall, axillary, supraclavicular, infraclavicular and ipsilateral internal mammary nodes. Of great concern, however, was the finding that this effect was almost entirely due to a major effect of systemic treatment on time to loco-regional progression rather than on time to distant metastasis. As a result only a non-significant trend in overall survival was seen in favour of the combined hormonal and chemotherapeutic treatment. Despite criticism with respect to the radiotherapy dose (46 Gy + 14 Gy boost) and the possibly suboptimal chemotherapy regimen (CMF), this trial has underlined one important point: we still do not know whether systemic treatment for LABC has the potential to improve long-term cure rate or simply to increase the time to treatment failure. Tumour cell kill of distant micrometastases clearly remains a major obstacle in the treatment of LABC.

Because there is rather compelling evidence from the 1980–1990 published literature that systemic therapy has contributed to the improved local control which is now in the range of 60–80% and the extended relapse-free survival in LABC [4–8], two endpoints which affect the quality of life of breast cancer patients, most oncologists will endorse the use of systemic therapy in the management of this disease. However, if cure rate is only minimally affected by the use of currently available cytotoxic agents, the main goal of therapy should be the longest possible disease control with the least toxic treatment.

In our "meta-analysis era" [9], there is usually hope that, by pooling the results of a number of randomised clinical trials such as the one performed by the EORTC Breast Cancer Cooperative Group, one can demonstrate a small but significant impact of systemic treatment on survival of LABC. Because such trials are nonexistent, however, we will have to live with this dilemma concerning the true contribution of hormonal and/or chemotherapy to the outcome of this heterogenous subset of breast cancer patients.

Table 1 shows that the only other trial designed to assess the value of systemic treatment in LABC [10] had too few patients to detect a significant difference in survival. As for the EORTC study, the majority of patients had non-inflammatory breast cancer and hormonochemotherapy consisted of tamoxifen com-

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Table 1. Prospective randomised clinical trials for LABC variable = systemic therapy

Reference	Disease entity	No. patients	Study design	Results
2	Non infl ≫ infl No–3	363	RT RT + HT RT + CT RT + HCT	Systemic treatment prolongs time to progression, mainly loco-regional progression
10	Non infl > infl No–2	118	RT HCT HCT→ RT→ HCT	Same 5 years RFS and OS in all arms
11	Operable LABC (T3 No–2 = 85%)	119	RT CT RT + CT	RT + CT has improved local control and 5 years OS

RT, radiotherapy; HT, hormonotherapy; CT, chemotherapy; HCT, hormonochemotherapy; OS, overall survival; RFS, relapse free survival.

bined with CMF. The positive trial published by Klefstrom *et al.* [11] looked at a very favourable subset of operable "LABC": 85% of patients had T3 N0–N2 tumours. The chemotherapy regimen consisted of six cycles of vincristine, doxorubicin, cyclophosphamide and levamisole (the latter given to 50% of the patients), and was found to increase disease-free survival and overall survival.

SYSTEMIC TREATMENT FOR LABC: WHEN?

The optimum interfacing of local and systemic therapies for LABC remains undefined. Only one relatively small randomised clinical trial (113 patients) [12] addressed this question (Table 2) and found no difference between radiotherapy first or chemotherapy first. A detailed analysis of this trial has not been published.

In a few "pilot" studies, systemic chemotherapy has been given simultaneously with radiation therapy [13–15]. Although local disease control and overall survival appear similar to that obtained when the two modalities are given sequentially, treatment toxicity may be enhanced and delivery of full doses of chemotherapy compromised [13].

The most popular treatment sequence has undoubtedly become systemic treatment first: not only does it facilitate loco-regional therapy but it gives the medical oncologist an extraordinary opportunity to assess the clinical and pathological aspects of tumour response to different cytotoxic drugs and regimens. The hope, here, is to identify a drug combination that will result in the highest complete remission rate, with histological confirmation whenever possible. The next questions, then, become: for how long should this therapy be applied to responsive patients? and should it be stopped or modified in non-responsive patients?

SYSTEMIC TREATMENT FOR LABC: FOR HOW LONG?

The important issue of treatment duration has not been solved for LABC.

For "induction" chemotherapy, two treatment policies are encountered: either a fixed number of 3–6 cycles or a flexible number according to time to "best response".

The role of maintenance hormono- or chemotherapy after locoregional treatment is still debatable: the only small controlled randomised clinical trial which explored the value of continuing the same chemotherapy regimen after radiotherapy in responsive patients found an increased relapse-free survival in favour of the maintenance arm (Table 2) [16].

Interestingly, duration of treatment remained of prognostic importance in the analysis of the long-term (10-year) results of this study [17]. Since early results showed that maintenance chemotherapy affected local progression free-survival more than distant progression-free survival, this may suggest that, in a subset of patients, optimal and prolonged locoregional disease control could have an impact on long-term survival.

An ongoing randomised clinical trial tests the value of different and possibly non-cross-resistant maintenance therapy in patients with a poor response to induction therapy (Table 2) [18].

SYSTEMIC TREATMENT FOR LABC: HOW DO WE OPTIMISE CHEMOTHERAPY RESPONSE?

Since the late 1970s, many attempts have been made to optimise systemic therapy for LABC by the use of complex multi-drug regimens, combination of chemotherapy with hormonal agents given as potential "synchronisers" of tumour cells, and, more recently, high-dose chemotherapy with or without autologous bone-marrow transplantation (ABMT) and haematopoietic growth-factors. Because of the uncontrolled nature of most of these studies, much controversy remains as to the optimal systemic treatment for LABC.

The role of hormonal manipulation, alone or combined with chemotherapy, has only been properly evaluated in the large EORTC randomised trial mentioned previously [2] which showed the greatest effect on local progression-free survival of the combined modality regimen.

A small randomised Italian study found a detrimental effect of the combination of tamoxifen and CMF on survival (Table 2) [19] but this could have occured by chance alone. A small, randomised Australian study found no difference in the 3 year relapse free survival when continuous tamoxifen was compared with 10 cycles of a FAC regimen (Table 2) [20].

In all these studies, the proportion of inflammatory breast cancers was very small. In this subset of LABC, which is often oestrogen and progesterone receptor-negative [21], the contribution of hormonal treatment to chemotherapy still requires clarification.

Considerable interest has been generated in the 1980s by the concept of hormonal recruitment of cancer cells into the S-phase, which should increase their sensitivity to cycle-specific chemotherapy agents. This strategy was employed by the NCI in a large phase II study [22] where synchronisation through tamoxifen and premarin given in sequence preceded chemotherapy with methotrexate and 5-fluorouracil (5FU) and followed administration of doxorubicin and cyclophosphamide. A recent update of this study [23], which accrued 100 patients with LABC, confirmed the very high complete clinical and pathological response rates initially reported of 46 and 27%, respectively. Unfortunately these unusually high complete response rates did not translate into improved survival. The only randomised trial, by Conte *et al.* [24], exploring the potential benefit of hormonal recruitment in inflammatory breast cancer prospectively, did not have the power to detect a difference in outcome between the two arms (Table 2). However, the

Table 2. Prospective randomised clinical trials for LABC variable = type, timing or duration of systemic therapy

Reference	Disease entity	No. of patients	Question	Design	Results
12	Infl + non infl	113	Best sequencing	R → CMFP–RT–CMFP; RT → CMFP	Same median survival (2 years)
16	Infl + non infl	110	Role of maintenance	AV × 4–RT → AV × 6; 0	Increased RFS for maintenance
18	Infl + non infl	193	Role of non cross-resist. maintenance	VACP × 3–SX–R → Same CT → RT; VMF → RT	Too early
19	Non infl ≫ infl	49	Role of hormonal manipulation in combination	R → CMF → SX → CMF; CMFT → SX → CMFT	Diminished OS survival for CMFT ! (P 0.05)
20	Non infl, postmenopausal only	71	Hormone or chemo	R → Tam; FAC × 10	Same RFS at 3 years
24	Infl + non infl	86	Role of hormonal recruitment	R → Fac × 3–loc.tr.–FAC + CMF; E_2FAC × 3–loc.tr. E_2FAC/E_2CMF	Same OS at 4 years
25	Non infl	41	Role of anthracycline	SX–R → CAF → CMFVP × 6; CMFVP × 12	Trend for better RFS for CAF (P = 0.05)

A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; M, methotrexate; R, randomisation; RT, radiotherapy; SX, surgery; P, prednisone; V, vincristine; E_2, diethylstilboestrol; OS, overall survival; RFS, relapse-free survival; Loc.tr., local treatment.

comparable response rate observed between FAC chemotherapy alone or preceded by a "pulse" or diethylstilboestrol suggests that different strategies for inducing hormonal recruitment may be required.

On both sides of the Atlantic, doxorubicin containing regimens are preferred although only one small randomised clinical trial looked at the potential benefit of a doxorubicin containing combination over a non-doxorubicin containing one (Table 2) [25].

SYSTEMIC TREATMENT FOR LABC: HOW AGGRESSIVELY?

Although Table 3 may suggest that the highest complete responses are seen with the more "intensive" doxorubicin-containing regimens [16, 26–30], the small differences in 4–5 year overall survival may be largely explained by differences in patient selection.

Encouraging short-term results have been reported in pilot studies where dosages of cyclophosphamide and/or 5-fluorouracil rather than doxorubicin were increased over the conventional dose range: Chevallier reported a 32% histologically confirmed complete response (CR) rate with an intensified FEC regimen in patients with inflammatory disease [31]. These results are impressive in view of the commonly reported 10% histological complete remission rate. In his series of 24 IBC patients receiving high-dose cyclophosphamide and 5-fluorouracil in 5-day courses every 3 weeks for 2 years, Israel *et al.* [32] reported a 96% objective response rate of which less than 10% were complete, and a median survival in excess of 6 years.

Table 3. Doxorubicin (A)-based combination chemotherapy regimens for LABC

Reference	Disease entity (infl/non infl)	Chemotherapy regimen	Theoretical dose-intensity mg/m²/week	No. patients	Per cent response Total/CR	Survival
26	Both	CAFVP	12.5	113	69/NA	35% at 5 years
27	Infl	AVCMF	12.5	79	27/NA	74% at 4 years
28	Both	FAC	16.6	280	67–87/NA	50% at 2 years
29	Non infl	AV	20	132	54/6	50% at 4 years
16	Both	AV	25	110	70/15	59% at 4 years
30	Both	VeTMFAP	30	98	91/23	74% at 4 years

Infl, inflammatory; A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; V, vincristine; P, prednisone; M, methotrexate; Ve, vinblastine; T, thiothepa; CR, complete response.

Although retrospective data do suggest that the chemotherapy-dose is plausibly important in the treatment of breast cancer patients [33–36] the shape and the slope of the dose–response curve remain largely unknown.

Because the first generation of uncontrolled trials of high-dose chemotherapy with ABMT, performed in highly selected stage IV breast cancer patients, documented high response rates but few long-term survivors, a move to more intensive treatment upfront has occurred and several groups are now designing high-dose chemotherapy programs for stage III disease, including inflammatory carcinoma, and for resectable breast cancer with $\geq$10 histologically positive axillary lymph nodes.

Antman recently reported on 56 patients with inflammatory or non-inflammatory stage III breast cancer treated with high-dose chemotherapy as consolidation treatment following response to induction chemotherapy [37]. The follow-up is still too short to draw any meaningful conclusion.

At the University of Groningen [38] previously untreated premenopausal women with stage III breast cancer currently receive induction chemotherapy with doxorubicin, vincristine, methotrexate, 5-fluorouracil and prednisone and, if responsive, they undergo high-dose intensification with cyclophosphamide and etoposide, followed by ABMT. The programme is completed by locoregional radiotherapy and tamoxifen.

At the Milan Cancer Institute [39], the current approach is different: the final intensification phase with high dose melphalan + ABMT is preceded by a short induction phase including high-dose cyclophosphamide and high-dose methotrexate. There are two original aspects to this programme: the first is the use of a short-term, high-dose induction course instead of induction with repetitive courses of conventional dose regimens, a strategy which may minimise the risk of emergence of multiple-drug resistance; the second is the use of a haematopoietic growth-factor (rh GM-CSF) given after high-dose cyclophosphamide: this administration gives rise to an extremely high number of haematopoietic precursors in the blood which are then harvested by leukapheresis and given back to the patient together with her bone-marrow. The result is an extremely rapid and complete bone-marrow recovery, which should lower the morbidity and the 10–15% mortality associated with most programmes of high dose chemotherapy + ABMT [40, 41].

MULTIMODALITY TREATMENT OF LABC: PROGNOSTIC FACTORS?

Analysis of clinical variables which affect long-term results in large series of LABC patients treated with various forms of multidisciplinary approaches including chemotherapy has been carried out by three groups of investigators.

The MD Anderson Cancer Institute analysed variables in 136 patients with noninflammatory LABC (T3–4 a/o N2–3) who received preoperative chemotherapy followed by mastectomy and axillary dissection as part of a prospective protocol between 1974 and 1985 [42]. Univariate analysis revealed that the number of metastatic lymph nodes, clinical tumour stage at presentation, clinical and pathologic response and menopausal status were significant variables predicting for overall survival and disease-free survival. When evaluated by multivariate regression, surgical node staging, clinical tumour stage at presentation, clinical response and menopausal status proved to be the independent factors affecting outcome.

In the experience of the Milan NCI [17], involving 277 patients with locally advanced breast cancer of the non-inflammatory type, the variables significantly affecting the 10-year results were duration of treatment and tumour cell burden, expressed by size of primary tumour and clinical nodal status.

Table 4. Prognostic factors in locally advanced breast cancer treated with a multidisciplinary approach including chemotherapy

Non-inflammatory cancers
Tumour cell burden (expressed by tumour size and clinical nodal status [17] or clinical tumour stage at presentation [42]
Surgical node staging [42]
Clinical response to induction chemotherapy [42]
Menopausal status [42]
Treatment duration [17]
DNA ploidy [46]*
Inflammatory cancers
Size of erythema involving the breast [43, 44]
Clinical node staging [43, 44]
Presence or absence of oestrogen receptors [45]
DNA ploidy [46]*
Expression of C-*myb* and pS_2 genes [47]

*In this series, 57% of the patients had no systemic treatment.

At the Institut Gustave-Roussy [43], a multivariate analysis was performed on 332 inflammatory breast cancer patients treated between 1967 and 1987. Four independent negative prognostic factors were identified: postmenopausal (versus pre) status, diffuse (versus local) inflammatory breast, N2–N3 (versus N0N1) and the type of chemotherapy (ACM vs. AVCMF).

Size of erythema and clinical node staging were also found to be of prognostic value in a smaller series of 64 inflammatory breast cancer patients treated with neoadjuvant chemotherapy and radiotherapy [44].

Delarue and co-workers [45] measured oestrogen receptors (ER) in 59 clinically inflammatory tumours receiving hormono-chemotherapy as systemic treatment and found that the presence of ER was indicative of a more favourable prognosis.

The DNA pattern also predicted outcome in a group of 91 LABC patients, with an unclear but likely small proportion of inflammatory disease [46].

SYSTEMIC TREATMENT FOR LABC: PRIORITIES FOR THE NEXT DECADE?

With our expanding knowledge in the field of breast cancer molecular biology, one of our future priorities should be the refinement of prognostic factors for the inflammatory and non-inflammatory disease types.

Clinical parameters deserve further prospective analysis within randomised clinical trials. New biological markers, such as proto-oncogenes could more accurately predict the risk of relapse and help identify patients who need innovative forms of therapy. In this regard, it would be of interest to confirm recent data suggesting that concomitant expression of c-*myb* and pS2 genes in inflammatory breast cancer identifies a subset of patients with a potentially better prognosis [47]. The importance of a number of growth factors or growth factor receptors in the biology of breast cancer—which is now widely studied at the preclinical level—could also lead to the discovery of new prognostic factors or new therapeutic strategies [48].

The second priority for clinical research in the 1990s should be the design of large prospective randomised clinical trials which may need intergroup collaboration, in view of the rather

Table 5. Locally advanced breast cancer new randomised clinical trials for the 1990s

Group	Patient selection	Design of the trial
EORTC and NCIC	Stage III inflammatory	R → E E E E E E ⟶ (SX) + RT; C C C C C C Tam; q2w = 3m (+ G-CSF) / F F F F F F ⟶ (SX) + RT; E E E E E E Tam; C C C C C C; q4W = 6m
CALGB	Stage II (≥10 + LN) or III	R → CCC C→ C + ABMT→ RT; AAA* A CDDP Tam; FFF F BCNU; High dose / CCCC ⟶ C ⟶ RT; AAAA CDDP Tam; FFFF BCNU; Low dose

C, cyclophosphamide; A, doxorubicin; F, 5-fluorouracil; CDDP, cisplatin; RT, radiotherapy; Tam, tamoxifen; E, epidoxorubicin; SX, surgery; R, randomisation.
*Bone marrow harvest

low frequency of LABC in our Western world. Among the numerous questions about LABC for which we are still lacking a clear answer, probably the most urgent one to solve is the one related to the potential benefit of high-dose or high dose-intensity chemotherapy. Temptation will indeed be great, especially for rapidly growing tumours such as inflammatory breast cancers, to use aggressive chemotherapy regimens together with haematopoietic growth factors, which are already easily accessible to medical oncologists in several European countries. The increased morbidity and cost associated with high-dose or high dose-intensity chemotherapy is justified only if we can confirm the benefit of this fashionable strategy to the patient.

The EORTC Breast Cancer Cooperative Group has recently completed another interesting "pilot" trial of a repeat high dose-intensity course of myelosuppressive but not myeloablative chemotherapy in previously untreated breast cancer patients with LABC or stage IV disease [49]. The results of this trial show that, with the support of rh-G-CSF, it is possible to increase the dose-intensity of doxorubicin and cyclophosphamide, given at maximally tolerated doses, by shortening the interval between cycles from 3 to 2 weeks. This pilot study forms the basis of a future randomised clinical trial for inflammatory breast cancer outlined in Table 5. The high-dose intensity regimen will be compared with the "FEC" regimen used by the NCI Canada, as part of a neoadjuvant treatment program followed by loco-regional therapy and adjuvant tamoxifen: while cumulative doses of epidoxorubicin and cyclophosphamide will be very similar, their dose-intensity will be approximately doubled in the "intensive" arm using G-CSF.

Another important randomised clinical trial to be carried out by Duke University and the CALGB and outlined in Table 5 will try to determine whether high-dose myeloablative chemotherapy with ABMT has any clinical relevance to the treatment of LABC and poor-risk stage II disease (≥10 positive nodes) [50].

Finally, given the high incidence and morbidity of bone metastases in breast cancer patients, there may be an advantage to incorporate disphosphonates in (neo)adjuvant chemotherapy regimens for LABC and this question will be addressed in a future EORTC randomised clinical trial.

Proper patient entry into these trials should be the shortest route to find out whether "more is better".

With the above objectives on the priority list for the 1990s, we may learn a great deal in the area of LABC biology and treatment by the year 2000.

1. Arnold DJ, Lesnick GJ. Survival following mastectomy for stage III breast cancer. *Am J Surg* 1979, **137**, 362–366.
2. Rubens RD, Bartelink H, Engelsman E, *et al.* Locally advanced breast cancer. The contribution of cytotoxic and endocrine treatment to radiotherapy. *Eur J Cancer Clin Oncol* 1989, **25**, 667–678.
3. Haagensen CD. In: Haagensen CD, ed. *Diseases of the Breast.* Philadelphia, WB Saunders, 1971, 576–584.
4. Aackland SP, Bitran JD, Dowlatshahi K. Management of locally advanced and inflammatory carcinoma of the breast. *Surg Gynecol Obstetr* 1985, **161**, 399–409.
5. Canellos GP. The treatment of locally advanced breast cancer. *J Clin Oncol* 1984, **2**, 149–151.
6. McGuire WL, Abeloff MD, Hortobagyi GN, Swain SM. Treatment of stage III breast cancer. A panel discussion. *Breast Cancer Res Treat* 1989, **13**, 225–238.
7. Dorr FA, Bader J, Friedman MA. Locally advanced breast cancer: current status and future directions. *Int J Radiat Oncol Biol Phys* 1989, **16**, 775–784.
8. Swain SM, Lippman ME. Treatment of patients with inflammatory breast cancer. In: De vita VT, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology.* Philadelphia, JB Lippincott Company 1989, 129–150.
9. Peto R. Why do we need systematic overviews of randomized trials? *Stat Med* 1987, **6**, 233–240.
10. Schaarke-Koning C, Van der Linden EH, Hart G, Engelsman E. Adjuvant chemo- and hormonal therapy in locally advanced breast cancer: a randomized clinical study. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1759–1763.
11. Klefstrom P, Grohn P, Heinonen E, Holsti R, Holsti P. Adjuvant post-operative radiotherapy, chemotherapy and immunotherapy. *Cancer* 1987, **60**, 936–942.
12. Sponzo R, Gray R, Dam Sker JI, Tormey DC, Olsen JE, Cummings FJ. The management of non-resectable (stage III) breast cancer. *Proc ASCO* 1983, **2**, 110.

13. Piccart MJ, De Valeriola D, Paridaens R, *et al.* Six-year results of a multimodality treatment strategy for locally advanced breast cancer. *Cancer* 1988, **62**, 2501–2506.
14. Perez CA, Presant C, Philpott G, Ratkin G. Phase I–II study of concurrent irradiation and multi-drug chemotherapy in advanced carcinoma of the breast: A pilot study by the Southeastern Cancer Study Group. *Int J Radiat Oncol Biol Phys* 1979, 5, 1329–1333.
15. Meek AG, Order SE, Abeloff MD, Ettinger D, Robinson Baker R, Baral E. Concurrent radiochemotherapy in advanced breast cancer. *Cancer* 1983, **51**, 1001–1006.
16. Delena M, Zucali R, Viganotti G, Valagussa P, Bonadonna G. Combined chemotherapy – radiotherapy approach in locally advanced (T3b–T4) breast cancer. *Cancer Chemother Pharmacol* 1978, 1, 53–59.
17. Valagussa P, Zambetti M, Bonadonna G, Zucali R, Mezzanotte G, Veronesi U. Prognostic factors in locally advanced inflammatory breast cancer – long-term results following primary chemotherapy. *Breast Cancer Res Treat* 1990, **15**, 137–147.
18. Hortobagyi G, Holmes F, Frye D, Ames F, Tashima C, Buzdar A, McNeese M, Balch C. Comparison of two adjuvant chemotherapy programs for locally advanced breast cancer: a prospective randomized trial. *Proc ASCO* 1990, **9**, 21.
19. Coconi G, di Blasio B, Bisagni G, Alberti G, Botti E, Anghinoni E. Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. *Am J Clin Oncol* 1990, **13**, 226–232.
20. Alagaratman TT, Wong J. Tamoxifen versus chemotherapy as adjuvant treatment in stage III breast cancer. *Aust NZ J Surg* 1986, **56**, 39–41.
21. Keiling R, Guiochet N, Calderoli H, *et al.* Preoperative chemotherapy in the treatment of inflammatory breast cancer. In: *Primary Chemotherapy in Cancer Medicine*. New York, Alan R. Liss 1985, 95–104.
22. Sorace RA, Bagley CS, Lichter AS, *et al.* The management of nonmetastatic locally advanced breast cancer using primary induction chemotherapy with hormonal synchronization followed by radiation therapy with or without debulking surgery. *World J Surg* 1985, **9**, 775–785.
23. Lippman ME, Swain SM, Egan EF, Danforth DN, Bader J, Steinberg SM. Neoadjuvant chemotherapy in the combined modality approach of locally advanced non metastatic breast cancer. Meeting abstract, Second International Congress on neoadjuvant chemotherapy, Paris, 19–21 Feb. 1988, 8.
24. Conte PF, Gardin G, Miglietta L, *et al.* Chemotherapy with estrogenic recruitment in locally advanced and metastatic breast cancer: results of two randomized trials. *Proc ASCO* 1990, **9**, 43.
25. Casper ES, Guidera CA, Bosl GJ, *et al.* Combined modality treatment of locally advanced breast cancer: adjuvant combination chemotherapy with and without doxorubicin. *Breast Cancer Res Treat* 1987, **9**, 39–44.
26. Perloff M, Lesnick GJ, Korzun A, *et al.* Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a cancer and leukemia group B study. *J Clin Oncol* 1988, **6**, 261–269.
27. Rouesse J, Friedman S, Sarrazin D, *et al.* Primary chemotherapy in the treatment of inflammatory breast carcinoma: a study of 230 cases from the Institut Gustave-Roussy. *J Clin Oncol* 1986, **4**, 1765–1771.
28. Hortobagyi GN, Buzdar AV, Anes FC, McNeese MD. Neoadjuvant chemotherapy in the management of advanced primary carcinoma of the breast. Meeting abstract – Second International Congress on neoadjuvant chemotherapy, Paris, 19–21 Feb. 1988, 7.
29. Delena M, Varini M, Zucali R, *et al.* Multinodal treatment for locally advanced breast cancer. Results of chemotherapy-radiotherapy versus chemotherapy-surgery. *Cancer Clin Trials* 1981, **4**, 229–236.
30. Jacquillat Cl, Baillet F, Weil M, *et al.* Results of a conservative treatment combining induction (neoadjuvant) and consolidation chemotherapy, hormonotherapy and external and interstitial irradiation in 98 patients with locally advanced breast cancer (IIIA-IIIB). *Cancer* 1988, **61**, 1977–1982.
31. Chevallier B, Roche H, Olivier JP, Hurteloup P. Inflammatory breast cancer: intensive chemotherapy (FEC-BC) results in a high histologic complete response rate. *Proc ASCO* 1990, **9**, 42.
32. Israel L, Brean JL, Morere JF. Two years of high-dose cyclophosphamide and 5 fluorouracil followed by surgery after 3 months for acute inflammatory breast carcinomas. *Cancer* 1986, **57**, 24–28.
33. Hryniuk W and Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984, **2**, 1281–1288.
34. Hoogstraten B, George SL, Samal B, *et al.* Combination chemotherapy and adriamycin in patients with advanced breast cancer. A Southwest Oncology Group Study. *Cancer* 1976, **38**, 13–20.
35. Carmo-Pereira J, Oliveira Costa F, Henriques E, *et al.* A comparison of two doses of adriamycin in the primary chemotherapy of disseminated breast carcinoma. *Br J Cancer* 1987, **56**, 471–473.
36. Tannock IF, Boyd NF, DeBoer G, *et al.* A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–1387.
37. Antman K, Gale RP. Advanced breast cancer: high-dose chemotherapy and bone-marrow autotransplants. *Ann Intern Med* 1988, **108**, 570–574.
38. Willemse PHB, de Vries EGE, Sleiyfer DT, *et al.* Intensive induction chemotherapy and intensification with autologous bone marrow reinfusion in patients with stage IIIB and IV breast cancer. *Breast Cancer Res Treat* 1988, **12**, 147 (abstract).
39. Gianni AM, Bonadonna G. High-dose chemo- radiotherapy for sensitive tumors: is sequential better than concurrent drug delivery *Eur J Cancer Clin Oncol* 1989, **25**, 1627–1630.
40. Gianni Am, Bregni M, Siena S, *et al.* rh-GM-CSF reduces hematologic toxicity and widens clinical applicability of high-dose cyclophosphamide (7 g/m^2) treatment in breast cancer and non-Hodgkin's lymphoma. *J Clin Oncol* 1990, **8**, 768–778.
41. Gianni AM, Siena S, Bregni A, *et al.* Granulocyte–macrophage colony-stimulation factor to harvest circulating hematopoietic stem cells for autotransplantation. *Lancet* 1989, 580–585.
42. McCready DR, Hortobagyi GN, Kan Shu W, Smith Terry L, Buzdar AU and Balch ChM. The prognostic significance of lymph node metastases after preoperative chemotherapy for locally advanced breast cancer. *Arch Surg* 1989, **124**, 21–25.
43. Tursz T, Spielmam M, Le Chevalier T, *et al.* Prognostic factors in 332 inflammatory breast cancer patients (IBC). A 20 year experience at the Institut Gustave-Roussy. *Proc ASCO* 1991, **10**, 43.
44. Chevallier B, Asselman B, Kunlin A, Veyret C, Bastit Ph, Graic Y. Inflammatory breast cancer. Determination of prognostic factors by univariate and multivariate analysis. *Cancer* 1987, **60**, 897–902.
45. Delarue JC, May-Levain F, Mourizsse H, Contesso G and Sancho-Garnier H. Oestrogen and progesterone cytosolic receptors in clinically inflammatory tumors of the human breast. *Br J Cancer* 1981, **44**, 911–916.
46. Arnelöv C, Emdin SO, Roos G, Angström T, *et al.* Prognostic factors in locally advanced breast cancer (T3, T4) with special reference to tumor cell DNA content. *Acta Oncol* 1988, **27**, 221–226.
47. Guerin M, Lê MG, Travagli JP, Riov G. Expression of c-*myb* and pS2 genes in inflammatory breast cancer: association with a longer relapse-free survival of patients. *Proc ASCO* 1989, **8**, 30.
48. Piccart MJ, Devleeschouwer N, Leclercq G, L'Hermite M. A review of the local growth factors involved in the biology of breast cancer and their potential clinical interest. *Bull Cancer* 1991, **78**, 215–227.
49. Piccart MJ, Van der Schueren E, Bruning P, *et al.* High dose-intensity chemotherapy with epiadriamycin, cyclophosphamide and r-metHuG-CSF: an exciting new treatment approach for locally advanced and metastatic breast cancer. Meeting abstract. Fifth EORTC Breast Cancer Working Conference, Leuven, 4–6 Sep. 1991 (In press).
50. Shapiro ChL, Henderson IC. High-dose chemotherapy with autologous bone marrow transplantation for breast cancer: promise and perspective. *Oncol J Club* 1990, 2, 12–14.