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Perspectives and Commentaries

Salvage Therapy in Advanced Breast Cancer

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(A COMMENT ON: Howell A, Morrison J M, Bramwell V H C, Harland R N L, Moneypenny I J. Dibromodulcitol, mitomycin C and vinblastine (DMV) chemotherapy in advanced breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 873-876.)

BREAST cancer has a great propensity to metastasize and, once this dissemination has occurred, the disease cannot be cured with treatment modalities presently available. During the last two decades, numerous cytotoxic drugs and various new forms of endocrine therapy have become available. Their efficacy is unfortunately limited and the remissions that they may induce are generally short-lived. During the course of their disease, most patients will require a second- and even a third-line salvage therapy, which may influence the duration and the quality of their survival. After the publication in this journal of an article from Howell *et al.* [1] describing a new empirical combination chemotherapy regimen giving favorable results, even in heavily pre-treated patients, we seized the opportunity to review several aspects of salvage therapy in advanced breast cancer. Our aim is to provide guidelines for a rational selection of the most appropriate alternative treatment for a given patient and also to evaluate the results to be expected therewith.

The first question to answer is whether one should use an endocrine treatment or chemotherapy, or even a combination of both modalities. In order to provide the maximum benefit to the patient, the ultimate decision will take into account the chances of success of these various approaches and their possible side-effects. The main hormonal treatments of established efficacy in postmenopausal women are either tamoxifen, or aminoglutethimide plus a glucocorticoid, or medroxyprogesterone acetate. In premenopausal women, surgical castration is the classical modality, generally considered as the first choice, although recent reports indicate that tamoxifen might be effective as well when the ovarian function remains intact. All these treatments are of approximately equal value and achieve objective remissions in 30-40% of the patients, when used as first endocrine maneuvers.

A useful selection of the patients most likely to respond to hormonal treatments can be determined on the basis of the patients' clinical backgrounds. Advanced age, menopause occurring at least 10 yr previously, disease-free interval exceeding 2 yr or metastases limited to bone or to soft tissue only all represent conditions under which endocrine therapy can be effective. It is also particularly important to take into account the type of response to a previous hormonal treatment, as illustrated in a randomized cross-over study published by Harvey *et al.* [2], comparing tamoxifen with aminoglutethimide. In this trial, in accordance with what had been observed earlier with other modalities of hormonotherapy, it was found that tamoxifen responders had a better chance (44%) of achieving a second remission with aminoglutethimide than non-responders (7%). Similarly, in the other arm of the study, tamoxifen given as salvage therapy yielded 31 and 18% remissions respectively in patients who had responded or failed to respond to first-line aminoglutethimide respectively.

More predictive than clinical data, estrogen receptor (ER) and progesterone receptor (PR) assays performed on the primary tumor or on a biopsy of metastases are likely to provide useful information on the hormone-dependency of any

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breast cancer. Thus tumors lacking receptors are almost invariably refractory to endocrine manipulations and therefore represent good indications for chemotherapy; tumors containing at least one type of receptor and those containing both types may respond favorably to hormonal treatments in about 40 and 70% of the cases respectively. In addition, we have shown that the quantitative measurement of ER offers particular advantages by demonstrating that the probability of achieving an objective remission is positively correlated with ER concentration. We developed a predictive model based on ER concentration and clinical data which allows us to evaluate with considerable accuracy the chances for any patient to respond to a hormonal treatment [3].

To conclude the indications of endocrine treatments, let us recall that patients presenting a very high tumor burden with massive infiltration of viscera, i.e. the liver or the lung, respond very rarely to such maneuvers, at least when these are the only modalities to be used. In such a life-threatening situation a vigorous chemotherapy must be undertaken, consisting preferably of two or three cytotoxic drugs, chosen among those with established antineoplastic activity. In view of their lack of hematologic toxicity, a hormone or an antiestrogen (tamoxifen) might be associated with chemotherapy in the hope of increasing its immediate efficacy.

As regards chemotherapy, whatever the drugs to be used are, clinicians should keep in mind that dosage and schedule might greatly influence the success of the treatment. This statement is particularly well illustrated by the results obtained by Hoogstraten *et al.* [4] with the CMFVP regimen, either used as first-line treatment or after adriamycin failure. As shown in Table 1, an intensive weekly schedule did, in both instances, provide higher remission rates than did a less aggressive intermittent regimen utilizing the same five drugs. Various therapeutic schedules potentially useful as salvage treatments have been described in the literature. The results are, however, very discordant: a treatment found to be very effective by some might be declared totally devoid of interest by others. Two main explanations for these discrepancies are on one hand the heterogeneity of patient populations and on the other hand the lack of standardized methods for evaluation and reporting data.

A constant feature observed with systemic anticancer treatments is the dramatic reduction of their efficacy in multitreated patients. Both randomized cross-over studies comparing various popular regimens of chemotherapy (CMF vs AV [5] and CMFVP vs A, [4], of which the results have been summarized in Table 1, confirm this rule in advanced breast cancer. A similar observation was also made by Howell *et al.* [1], with their original combination of dibromodulcitol plus mitomycin C plus vinblastine (DMV). This treatment was first tested in 16 patients who had been previously treated with various regimens of chemotherapy, including six patients previously treated for an adjuvant purpose. Six objective remissions (37%) were obtained, with relatively low toxicity, so that the authors decided to test this treatment in a series of 24 previously untreated patients. Among the latter, the observed remission rate was 66%, which compares favorably with figures achieved by means of the most currently used 'standard' first-line regimens, e.g. CMF, CMFVP, AC or CAF (see Tables 1 and 2 for definitions). The ultimate demonstration of the eventual superiority of DMV over one or more of the latter would require a randomized comparative study involving a large number of patients.

After patent failure of treatment with hormones and cytotoxic drugs deemed to display the best antineoplastic activity, i.e. cyclophosphamide, methotrexate, fluorouracil and adriamycin (CAMF), one might expect that most tumors have in fact become strongly resistant to any further treatment. In such unfavorable cases encouraging results (20% remissions) were recently obtained with a combination of cisplatin plus vindesine tested by the EORTC Breast Cancer Cooperative Group [6]. Under almost similar conditions one might also consider the opportunity to use mitomycin C as single-drug therapy given at a high intermittent dosage, e.g. 12 mg/m^2 every 3 weeks [7]. It is as yet unknown whether the MDV regimen would yield better results than mitomycin alone. It is also not yet established whether the response rate of 37% observed by Howell *et al.* [1] in previously treated patients would be maintained at the same level in a homogeneous group of women all having tumors refractory to CAM and F. The same doubt exists about other two- or three-drug combinations involving mitomycin C, vinblastine, vindesine, thiotepa or dibromodulcitol [1, 8, 9], and about new compounds such as mitoxantrone and cisplatin analogs. Here again, additional studies are needed to confirm the efficacy of these potentially useful regimens and to establish their exact place in the therapeutic sequence which is likely to provide the best results in terms of response rate, duration of remission and total survival.

During the last 5 yr the particular problem of salvage therapy for recurrences occurring after systemic adjuvant treatments has become a new matter of preoccupation. As shown in the data summarized in Table 2, objective responses may be obtained with endocrine treatments or with

Table 1. Three randomized trials using a cross-over design in advanced breast cancer

Treatments under comparison*	Results when used as first line therapy: No. of patients	CR (%)	CR + PR (%)	Median duration of remission (months)	Results when used as second line therapy: No. of patients	CR (%)	CR + PR (%)	Median duration of remission (months)	Ref.
AGL + HC	34	6	47	18	32	3	19	6+	
vs									[2]
TAM	32	3	28	15	33	6	24	12.7	
CMF (8 cycles)	53	9.5	47	8	15	—	20	7.5	
vs									[5]
AV (8 cycles)	52	8	52	8.5	23	—	22	4.5	
CMFVP (intermittent)	98	8	40	9	24†	4	25	—	
vs									
CMFVP (weekly)	106	19	59	9	24†	8	46	—	[4]
vs									
A	79	4	39	4	49†	0	20	—	

*AGL = aminoglutethimide; A = adriamycin; C = cyclophosphamide; F = fluorouracil; HC = hydrocortisone; M = methotrexate; V = vincristine; P = prednisone.

†Patients treated with A as second-line therapy had previously been treated with CMFVP according to an intermittent or a weekly schedule; patients treated with CMFVP as second-line had all received A as first-line.

Table 2. Salvage chemotherapy for recurrences after adjuvant chemotherapy

Previous treatment	Salvage regimen Type	No. of patients	Response (%)	Median (months)	Ref.
Adjuvant CMF	HT	22	14	8	[10]
	AV	48?	41	10	[10]
	CAF	17	47	—	[11]
	CAF + TAM	13	38	—	[11]
	CMF	19	19	—	[12]
	HT	51	32	—	[12]
	A (combin.)	62	15	—	[12]
	VAM	15	53	5	[13]
Adjuvant AC	HT	10	30	11	[14]
	CMF	12	0	—	[14]
	AC(V)(HT)	11	45	6+	[14]

A = adriamycin; C = cyclophosphamide; F = fluorouracil; HT = hormonal treatment; M = methotrexate; V = vincristine; M = mitomycin.

various multiple drug combinations [10-14]. In a small series described by Chlebowski *et al.* [15], the survival of patients in relapse after adjuvant CMFVP was shorter than that of another group who had received a lighter prophylactic regimen using fluorouracil alone. The explanation for this impaired survival will remain a matter of speculation since salvage treatments were markedly different among the two groups, consisting mainly of A in the former and of CMFVP in the latter. Obviously, future adjuvant protocols should include guidelines for a standardized policy of treatment in case of recurrent disease. An important observation was made by Schapira *et al.* [12], who showed that relapses occurring after completion of adjuvant CMF could still respond to this combination. The results achieved with CMF (19% remissions) were similar to those obtained with A (15% remissions). Hence it must be concluded that resistance to one or more drugs may be affirmed only when overt disease progression has occurred under treatment,

provided that full dosage and an optimal schedule were used. It is in this situation only that a drug might reasonably be excluded from the panel of compounds potentially useful for a given patient.

From this brief review, it appears that the choice of an optimal treatment for recurrent breast cancer represents a difficult problem. The rather disappointing results obtained with all currently available salvage treatments should be the best motivation for oncologists to participate in clinical trials exploring new treatments or new therapeutic approaches. Within this framework of clinical experimentation, well-designed randomized studies are the most likely to provide useful information. They allow a direct comparison of two or more treatments given to similar populations of patients. When a cross-over design is adopted, they also yield an estimation of the cross-resistance between various regimens. Moreover, such randomized controlled studies are particularly appropriate for the screening of new drugs or new combinations. They will considerably reduce the risks of drawing false-negative conclusions which might lead to the rejection of an effective treatment, having been unfortunately tested among a population of patients bearing refractory tumors. In the particular setting of phase II trials, this relatively new methodology has now been adopted by many clinical cooperative groups working under the aegis of the EORTC.

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