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Drug Resistance in Clinical Practice: Patterns of Treatment Failure in Patients Receiving Systemic Therapy for Advanced Breast Cancer

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Abstract—*Strategies for overcoming the causes of drug resistance should take account of the patterns of treatment failure seen in clinical practice. We have analysed the patterns of disease progression in 267 patients with advanced breast cancer receiving systemic therapy. First disease progression on therapy most commonly occurred in tissues involved by tumour at the commencement of treatment. However in 40% of patients, first documentation of disease progression included a tissue not previously known to contain metastatic disease. In only 3% of patients was this new tissue the central nervous system. This pattern of disease progression was not influenced by treatment type (i.e. endocrine or cytotoxic), tumour response to treatment, oestrogen receptor status, prior adjuvant cytotoxic treatment, or disease free interval. These results question the wisdom of always ceasing existing therapy and substituting new treatment when progressive disease is first documented.*

INTRODUCTION

ACQUIRED drug resistance is a central problem in clinical cancer chemotherapy. While there is clearly a need for laboratory studies investigating the basis of tumour sensitivity to drug treatment, and changes which occur when a drug-sensitive tumour becomes resistant, additional data are also needed relating to the patterns of drug resistance seen in clinical practice. This latter information might lead to new strategies which delay treatment failure.

We have recently analysed the patterns of treatment failure in patients with advanced breast cancer treated at our institution. In 56 patients with metastatic breast cancer, first disease progression after systemic therapy most commonly occurred in tissues which contained metastases at the commencement of treatment [1]. However, in 23% of patients, initial disease progression was noted in a previously uninvolved tissue. Furthermore, no individual tissue type was associated with an apparently different pattern of treatment failure.

We now report the results of a similar analysis of the patterns of treatment failure in a much larger cohort of patients with advanced breast cancer receiving systemic treatment as participants in the Australian and New Zealand Breast Cancer Trials.

MATERIALS AND METHODS

The clinical trial records of 408 patients with advanced breast cancer were examined retrospectively. The cohort studied consisted of all patients entered on two randomized prospective multicentre clinical trials, conducted by the Australian and New Zealand Breast Cancer Trials Group, comparing different forms of cytotoxic or endocrine therapy [2, 3]. It was an eligibility requirement in these trials that the patients must have received no prior cytotoxic or endocrine treatment for metastatic disease. All sites of disease were documented before the commencement of randomized therapy. Baseline sites of disease were detected by clinical assessment and chest X-ray, and in the majority of cases radionuclide bone scans were also performed. Patients in whom additional metastatic sites were suspected were investigated further to document disease extent. The treatment regimens used in the trials from which the cohort was drawn are shown in Table 1. Individual tumour responses on therapy

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Table 1. Drug regimens used

Adriamycin	50 mg/m² day 1	repeat at 21
Cyclophosphamide	750 mg/m² day 1	day cycles (AC)
	or	
Endocrine — Tamoxifen	20 mg daily (postmenopausal)	
Endocrine — Oophorectomy	(premenopausal)	
	or	
Oophorectomy		
	or	
Cytotoxic + endocrine		

Table 2. Patterns of disease progression in advanced breast cancer

Patient group	No	Old	New*	Old + new
Tissue at first progression (%)				
Total	267	160 (60)	39 (15)	68 (25)
Tissue at second progression (%)				
Total	122	65 (53)	24 (20)	33 (27)

*Seven cases relapsed within central nervous system.

were categorized according to WHO criteria [4], and all sites of treatment failure were recorded. The major endpoint of the current analysis was identification of the tissue (e.g. bone, liver, etc.) in which disease progression was first recorded, and its relationship to tissues involved prior to systemic therapy. In addition, the influence on patterns of treatment failure of treatment type (endocrine or cytotoxic), tumour response, time to disease progression, and prior adjuvant therapy were investigated.

RESULTS

Of the 408 patients entered on the trials, 141 (35%) were not evaluable for this analysis (20 were ineligible for the protocol on which they were entered, 11 have not yet relapsed, 19 have died without assessment of disease status, 89 patients withdrew from trial treatment from drug intolerance or other causes, and in two cases trial records were incomplete).

In 267 patients it was possible to determine whether the first disease progression on trial treatment occurred in a tissue which was known to be involved by tumour at the commencement of therapy (i.e. an 'old' tissue), in a previously uninvolved tissue (i.e. a 'new' tissue), or both old and new tissues simultaneously. As shown in Table 2, first disease progression most commonly occurred in tissues involved by tumour at the commencement of therapy. However in 40% of patients, disease progression included a tissue not previously known to contain metastatic disease. In only seven patients (i.e. 3%) was this new tissue the central nervous system.

One hundred and twenty-two patients, after progressing on their initial randomized treatment, were evaluable for tissue of treatment failure on a subsequent therapy. As shown in Table 2, disease progression on 'second line' therapy followed the same pattern as first relapse on treatment.

Table 3 shows the tissue in which treatment failure was first documented according to the type of systemic therapy given, i.e. endocrine, cytotoxic or combined therapy. The tissue patterns of treatment failure were not apparently influenced by the type of treatment. Similarly, the oestrogen receptor status did not alter the patterns of treatment failure (see Table 3).

The tissue of first disease progression after systemic therapy, according to tumour response category, is also shown in Table 3. The patterns of tumour progression within each response category did not differ from that seen in the total group. Moreover, in 23 patients who had achieved a complete tumour response, the pattern of subsequent relapse did not differ significantly from that of the overall group.

Table 4 presents the tissue of first disease progression according to time elapsed since the initiation of randomized therapy (i.e. less than or greater than 6 months). No relationship between the pattern of treatment failure and time elapsed since commencement of therapy was apparent.

The tissue patterns of treatment failure were not detectably influenced by varying disease free

Table 3. Patterns of disease progression in advanced breast cancer

Patient group	Total	Tissue at first progression (%) Old	New	Old + new
Treatment				
Endocrine*	113	72 (64)	15 (13)	26 (23)
Cytotoxic	80	45 (56)	14 (18)	21 (26)
Combined	74	43 (58)	10 (14)	21 (28)
Oestrogen receptor status				
ER + ve†	26	19 (73)	2 (8)	5 (19)
ER − ve	50	29 (58)	8 (16)	13 (26)
Response to protocol treatment				
Complete response	23	16 (70)	4 (17)	3 (13)
Partial response	90	46 (51)	13 (14)	31 (34)
Stable disease	113	72 (64)	18 (16)	23 (20)
Progressive disease	41	26 (63)	4 (10)	11 (27)

*Oophorectomy 19 cases, tamoxifen 94 cases.
†Oestrogen receptor (ER) positive > 10 fmol/mg protein.

Table 4. Patterns of disease progression in advanced breast cancer

Patient group	Total	Tissue at first progression (%) Old	New	Old + new
Disease progression				
< 6 Months	128	81 (63)	20 (16)	27 (21)
> 6 Months	139	79 (57)	19 (14)	41 (29)
Prior therapy				
None	239	143 (60)	37 (15)	59 (25)
L-PAM	19	12 (63)	1 (5)	6 (32)
*Disease free interval**				
0‡	46	26 (57)	6 (13)	14 (30)
≤ 2 years	98	60 (61)	18 (18)	20 (20)
> 2 years	123	74 (60)	15 (12)	34 (28)
Patient survival				
< 1 year	66	34 (52)	12 (18)	20 (30)
1–2 years	84	48 (57)	12 (14)	24 (29)
> 2 years	117	78 (67)	15 (13)	24 (21)

*DFI = interval between mastectomy and first disease recurrence.
†Presented with metastatic disease.

interval or the prior administration of adjuvant cytotoxic therapy. The data for patient survival from the time of beginning systemic therapy are also shown in Table 4. The same overall pattern of treatment failure was observed in patients with widely differing survival duration.

DISCUSSION

Strategies for overcoming the causes of treatment failure should be based upon an analysis of why failure occurred. In a previous study of 56 patients receiving systemic therapy for advanced breast cancer, we reported that in approximately half of the cases studied the first evidence of tumour progression occurred in a site (n.b. not necessarily a new tissue) that had not previously been recognized to contain metastases [1]. The observation that relapse in new sites is a frequent pattern of treatment failure has now been confirmed in a much larger patient cohort. Whilst disease progression on systemic (either cytotoxic or endocrine) therapy most commonly occurred in previously involved tissues, in 40% of patients disease progression involved a new tissue. In 15% of cases, disease progression occurred only in new tissues. Furthermore, no individual tissue type was apparently different in this regard (data not shown). Under these circumstances, where possible, it is appropriate to add a new therapy to control the new site of disease, rather than substitute for the initial treatment. This may involve local irradiation of isolated new sites of disease while continuing previous systemic therapy,

or the addition of other systemic agents (either endocrine or cytotoxic) to the existing regimen.

The same pattern of treatment failure was observed in cohorts defined according to the response to treatment, when progression occurred, the administration of adjuvant cytotoxic therapy, oestrogen receptor status, and the type of systemic therapy (*viz* endocrine, cytotoxic or combined). Our observations are at variance with the reported patterns of relapse (off treatment) in patients with Hodgkin's disease [5], germ cell [6] and childhood tumours [7]. In these tumour types bulk sites predominate as the initial site of progression following a complete response. This latter pattern is also reported in patients with advanced breast cancer relapsing after a complete response to systemic therapy [8]. We presume that drug access and/or cell kinetic factors are the predominant bases of treatment failure in extremely drug-sensitive tumours which usually grow rapidly. On the other hand, in the more common adult tumour types, where complete tumour responses are relatively uncommon, the pattern of treatment failure is clearly more heterogeneous. It is notable, however, that relapse following adjuvant chemotherapy in breast cancer may be more akin to drug sensitive and childhood tumour types, since it is reported that re-introduction of the 'failed' adjuvant therapy frequently causes tumour regression [9].

Measurement error may play a small part in the pattern of treatment failure we have observed, since small new lesions may be easier to detect than changes of similar volume in the known larger masses. However, if the results are taken at face value, one presumes that the new disease sites have developed during treatment from previously undetected micrometastases. We infer that these new sites of disease contain cell clones that are less sensitive to growth inhibition by the administered drugs than those existing in the old sites. This scenario is compatible with the somatic mutation theory of drug resistance if one draws an analogy with the classic fluctuation analysis of Luria and Delbruck [10]. As Goldie and Coldman have pointed out [11], one could imagine ten separate 0.6 cm lesions distributed throughout the body, all clinically undetectable. The chances of at least one of these undetected metastases containing a significant proportion of resistant cells would be equal to that of finding the same number of resistant cells in a single 6 cm deposit.

An alternate explanation for frequent disease progression in new sites is that tumour clones with differing drug resistance profiles flourish in different tissues. Only laboratory studies comparing characteristics of tumour specimens from both the old and new sites of disease will resolve this question.

It cannot be assumed that tumour progression in a new tissue or site is necessarily an isolated 'clonal' event, rather than a function of pharmacokinetic differences between tissues. The latter explanation is probable in the identification of the central nervous system [12] and testis [13] as drug sanctuary sites. The clinical observation that patients with alopecia occasionally experience regrowth of hair despite continuing cytotoxic treatment, in the face of myelosuppression with each cycle of treatment, suggests that tissue pharmacokinetic factors may be clinically important [14].

Although the bases of initial disease progression in a new site on systemic therapy are uncertain, this pattern of treatment failure is clearly common in advanced breast cancer. Possible means of delaying subsequent disease progression include a policy of adding to, rather than substituting for, initial treatment when disease progression is first documented. This may involve local irradiation of isolated new sites of disease while continuing previous systemic therapy, or the addition of other systemic agents (either endocrine or cytotoxic) to the existing regimen. Longitudinal study of such policies are needed and may clarify some of the bases of clinical drug resistance.

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