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Impact of Patient Characteristics on Treatment Outcome: Anthracycline Resistance

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In the treatment of breast cancer, anthracycline-containing combinations are frequently used as adjuvant therapy or to treat patients with metastatic disease. However, most patients with metastatic disease who are treated with these combinations develop progressive disease and a significant proportion of patients, after receiving anthracycline-containing adjuvant therapy, experience recurrent disease. Patients who develop recurrent disease while receiving adjuvant therapy and those whose metastatic disease progresses without an objective response while on treatment to control the disease, are among those defined as having primary refractory disease. These patients have a poor prognosis. In other patients whose breast cancer is treated with anthracycline-containing combinations, defining the degree of resistance requires careful consideration of the type of response to therapy (complete response, partial response or no change in disease status) the duration of response and, for patients in the adjuvant setting, the length of the disease-free interval. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

THE NATURAL history of breast cancer has changed over the past two decades [1, 2]. Following the introduction of combination chemotherapy, 60–80% of patients now achieve objective regression of disease and, of those, 20–25% have a complete response. The median duration of response (complete and partial) ranges from 9 to 12 months and the median length of survival varies from 21 to 24 months. This survival time is, on average, 9 to 12 months longer than that of patients whose breast cancer was treated with monotherapies prior to the introduction of systemic combination chemotherapy [1].

In the past two decades, anthracyclines (e.g. doxorubicin, epirubicin) have been among the most active drugs in the treatment of breast cancer. A number of studies comparing anthracycline- with non-anthracycline-based combinations in the treatment of metastatic breast cancer have shown that patients treated with anthracycline-containing combinations have a longer survival period than those receiving non-anthracycline-based chemotherapies [3–5].

In recent years, several new drugs, such as the taxoids, docetaxel (Taxotere®) and paclitaxel (Taxol®), have become available that have significant antitumour activity in patients with previously treated metastatic breast cancer, including those treated with anthracycline-containing combinations. Defining the extent and degree of resistance to prior chemotherapy or chemotherapies is imperative to assess and compare the efficacy of these newer drugs [6, 7].

The objective of this paper is to clarify the groups of patients with breast cancer who are resistant to anthracycline-based chemotherapy. The survival rates of patients treated at the M.D. Anderson Cancer Center with doxorubicin-containing chemotherapies, either as adjuvant therapy or as treatment for metastatic disease, is briefly described to illustrate the different prognoses of subsets of patients treated.

PATIENTS AND METHODS

Between 1974 and 1994 a consecutive series of 1898 patients was treated in adjuvant chemotherapy protocols containing doxorubicin. Of these patients, 734 (39%) subsequently developed metastatic disease.

The patients' pretreatment characteristics are included in Table 1. Of the 734 patients, 102 (14%) had recurrent disease within 12 months and 632 (86%) had metastatic disease >12 months after completion of adjuvant therapy. Thirty-seven per cent of patients had recurrences in the viscera and 30% developed osseous disease. The overall duration of survival was calculated from the date of recurrence. Overall survival curves were plotted following the Kaplan and Meier [8] method; differences between the curves were tested using the Gehan-Wilcoxon test [9].

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Table 1. Characteristics of 734 patients with breast cancer who developed metastatic disease after adjuvant therapy at the MD Anderson Cancer Center

	Time to recurrence (%)		
	≤12 months	>12 months	Total (%)
Total no. patients	102 (14)	632 (86)	734 (100)
Age (years)			
<50	50 (51)	312 (49)	364 (50)
≥50	50 (49)	320 (51)	370 (50)
Stage of breast cancer			
I	1 (1)	7 (1)	8 (1)
II	53 (52)	441 (70)	494 (67)
III	48 (47)	184 (29)	232 (32)
Dominant site of metastases			
CNS	11 (11)	55 (9)	66 (9)
Viscera	39 (38)	230 (36)	269 (37)
Bone	18 (18)	204 (32)	222 (30)
Soft tissue	34 (33)	127 (20)	161 (22)
Unknown	—	16 (3)	16 (2)

Between 1973 and 1982 another group of 1581 patients with metastatic breast cancer were treated with doxorubicin-containing chemotherapy. Of these, 1498 experienced progression of their disease; an objective response was assessed in 1475. Their survival from the time of progression on therapy was evaluated, according to the type of response to the initial therapy. The response to initial therapy was defined according to International Union Against Cancer (UICC) response criteria.

RESULTS

In the group given adjuvant therapy, those with a disease-free interval of ≤12 months generally had a worse prognosis than those whose disease-free interval was more than 1 year (Figure 1). However, 5 patients who had a recurrence <6 months after completion of chemotherapy survived for 5 years. The survival rate of this very small group was the same as that of patients with a disease-free interval of more than one year. Table 2 shows the length of survival, from the date of recurrence, in patients whose disease recurred after the completion of adjuvant therapy.

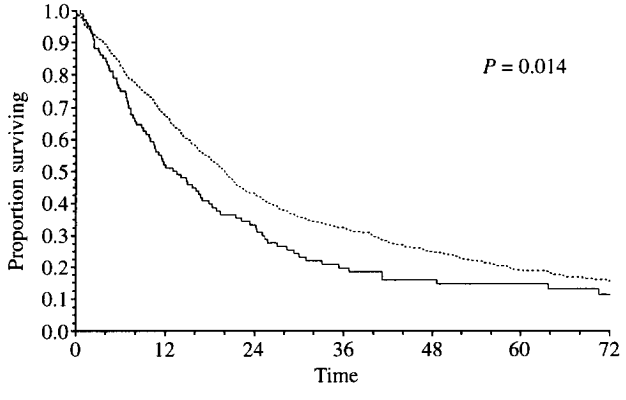

Figure 1. Survival rates, from the time of recurrence of breast cancer disease, in 734 patients treated with adjuvant therapy; patients are divided according to their disease-free interval. .....Disease-free interval >12 months. _____Disease-free interval ≤12 months.

Table 2. Survival rate of 734 patients who developed metastatic disease following anthracycline-based adjuvant therapy; survival is calculated from time of recurrence

Time to recurrence (months)	Number of patients	Survival rate (%) 1 year	2 years	3 years	5 years
≤12	102	52	32	19	14
0–5	28	57	31	23	18
6–12	74	48	31	16	12
>12	632	65	41	31	18

Table 3. Survival rates of 1475 patients treated with anthracycline-based chemotherapy for metastatic breast cancer; survival duration is calculated from the date of disease progression and the patients divided according to their response to initial therapy

Response	Number of patients	Survival rate (%) 1 year	2 years	3 years	5 years
Complete response	216	52	27	17	7
Partial response	754	40	17	9	3
No response	364	26	10	4	2
Progressive disease	141	11	5	2	1

Table 3 shows the survival, from the date of progression of disease, in the 1475 patients treated for metastatic disease. The patients are grouped according to their initial response to chemotherapy. Of these patients, 216 (15%) had a complete response, 754 (51%) a partial response, 364 (25%) experienced no change and 141 (9%) had progressive disease. Response status was not evaluated in 23 patients. At 3 years, the estimated survival rate for the complete response group was 17%, compared with 2% for patients with progressive disease.

DISCUSSION

Resistance to initial therapy can be categorised into three broad subgroups, dependent on the response to initial therapy; patients in each subgroup have a different prognosis (Figure 2).

Primary resistance

This may be one of the easiest subgroups to define and includes patients who develop metastatic disease while receiving anthracycline-based chemotherapy as adjuvant therapy, or whose disease progresses while they receive treatment to control their metastatic disease. Patients whose metastatic disease progresses during anthracycline-based therapy have the most dismal outcome. In our experience a large number of these patients treated with sequential doxorubicin-containing combinations, the median survival was 16 weeks from initiation of therapy. Patients who develop metastatic disease while receiving adjuvant therapy, or within 12 months of completing chemotherapy, also have a poor prognosis.

An earlier study by our institute reported a small subgroup of patients who developed asymptomatic osteoblastic metastases, without other evidence of metastatic disease, while on anthracycline-based adjuvant therapy [10]. These patients had no symptoms of bone pain and had a more favourable prognosis than patients with symptomatic metastases in the

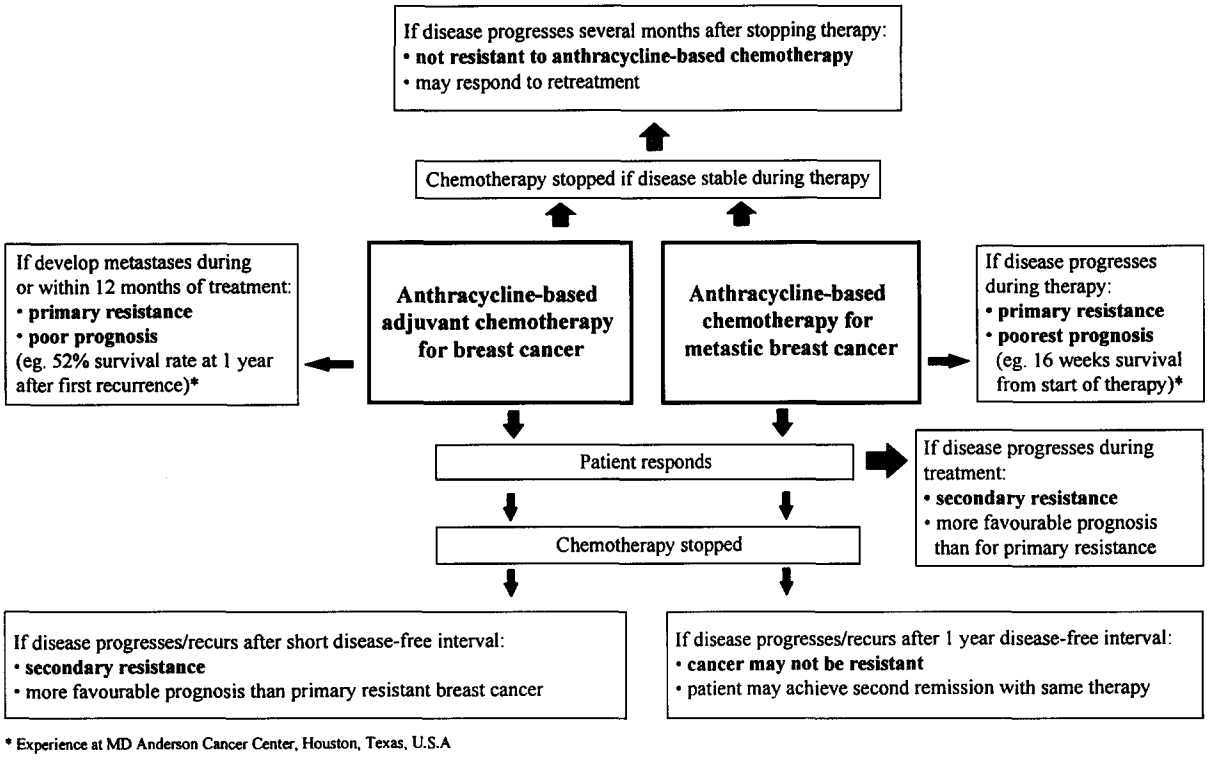

Figure 2. Schematic presentation of doxorubicin-resistance in patients with breast cancer.

bone or at other sites. Therefore, patients with occult osseous disease need to be differentiated from other patients in the primary resistance group. The occult osseous disease was not detected before chemotherapy began and the blastic healing that occurred was in response to initial chemotherapy. The presence of asymptomatic osteoblastic metastases should not be viewed as resistance to anthracycline therapy and the therapy should not therefore be changed. A diagnosis of resistance in this subgroup should be based on the development of symptomatology (i.e. bone pain) only, development of osteolytic metastatic disease or disease in non-osseous sites.

Progression of disease following discontinuation of chemotherapy

In earlier years, chemotherapy was continued until there was evidence of disease progression; but, in the past decade, there has been a trend towards stopping systemic chemotherapy after maximum regression of disease is achieved with cytotoxic therapy. Patients treated under this latter protocol, but whose disease subsequently progresses after chemotherapy is stopped, may achieve a second remission with the same therapy at the time of disease progression. Limited data suggest that the longer the progression-free interval, the higher the likelihood of a response to a repetition of the initial therapy [11]. Patients with a shorter disease-free interval are considered resistant to previous therapy.

Similarly, following adjuvant therapy, patients who develop recurrent disease more than 1 year after completing chemotherapy may respond to the same therapy and should not be considered resistant to previous adjuvant therapy before re-treatment with the same combination of drugs [12]. In our studies, a few patients have remained in prolonged remission while being treated with the same drugs that were included in their adjuvant therapy.

Patients with progressive disease after an initial response, while still on the same therapy, are also resistant to their therapy, but their prognosis is more favourable than that of patients with primary resistance to initial therapy. Patients with progressive disease after an initial response tend to respond to subsequent therapies more frequently than patients with primary resistant disease.

Stable disease on anthracycline therapy

In this subgroup of patients it is not feasible to determine response to therapy by using conventional objective criteria. These patients have evaluable disease only, which cannot be measured bi-dimensionally. Patients in this subgroup have stable disease during and after chemotherapy. For this subgroup, treatment guidelines similar to those used for patients with measurable disease should be followed. If therapy is stopped and the patient progresses several months after the last dose of chemotherapy, re-treatment with the same drugs may result in improvement. These patients should not be considered resistant to anthracycline-based therapy.

If patients have stable disease for several months while on therapy and the cancer subsequently progresses, they should have a similar prognosis to patients who respond initially to therapy.

CONCLUSIONS

Clear definition of a patient's anthracycline resistance status is imperative at the time of secondary treatment with cytotoxic drugs. Patients with primary resistance, either in the adjuvant setting or in metastatic disease, have a dismal outlook, while patients who develop secondary resistance have a more favourable prognosis and tend to respond to subsequent therapies more frequently. The pre-treatment characteristics

of patients, such as the stage of their disease and age, should be taken into account when comparing data from various clinical studies assessing new drugs in previously-treated patients.

Another issue to be considered is the dose intensity of these treatments. If patients receive suboptimal therapy, then it may not be resistance to therapy, but inadequate therapy, that causes a lack of response. Patients who have been treated with doses or schedules of drugs that are suboptimal may not have true resistance and could benefit from treatment with the same drugs at higher doses. They should receive appropriate anthracycline combinations which have been evaluated adequately in clinical trials.

Finally, a small proportion of patients who have failed one anthracycline regimen have been reported to respond to another anthracycline [1, 3], which illustrates the fact that resistance is not absolute between these drugs. It is not possible to evaluate whether patients in this report received the appropriate dose intensity in the first treatment combination.

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