Systemic treatment of metastatic breast cancer

Stephen RD Johnston

This article reviews recent advances in the treatment of metastatic breast cancer, in particular the results of randomized controlled phase III clinical trials. These have led to the evidence-based introduction of several new drugs including aromatase inhibitors, taxanes and bisphosphonates, some of which have been shown to impact on overall survival.

Women develop advanced metastatic breast cancer when there is recurrence of disease at distant sites including bone, liver, lung or soft tissue which is no longer treatable by surgery. Secondary tumours may develop despite systemic drug therapy having been given in the adjuvant setting where the aim was to eliminate micro-metastatic disease following primary treatment for early breast cancer.

With the increasing use of adjuvant endocrine and cytotoxic systemic therapies in early breast cancer, the interval since completion of such treatment and the development of metastases (disease-free interval) is important in determining whether metastatic disease is likely to be resistant to further systemic therapy, and which treatment options may be successful in the advanced setting (Rubens et al, 1994).

The goal of treatment for women with advanced metastatic breast cancer is palliation. Both endocrine therapy and chemotherapy are used to induce tumour regression, and as such these treatments relieve tumour-related symptoms in conjunction with supportive care measures. The choice of initial systemic treatment, in particular whether endocrine or chemotherapy is used first, is based on a variety of clinical factors (*Table 1*). At the same time the choice of specific drug or regimen for an individual patient is dependent on prior therapies received in the adjuvant setting, together with the likelihood of benefit balanced against a given drug's side-effect and tolerability profile for any given patient. Until the introduction of recent therapies, previous treatments for advanced breast cancer were considered to have minimal impact on overall survival.

ENDOCRINE THERAPY

Approximately two-thirds of human breast carcinomas express oestrogen receptors (ER) and thus may be dependent on oestrogen for their growth. Routine immunohistochemical assays on paraffin-embedded tissue mean that this information should now be available for all breast cancer patients (*Figure 1*). Tamoxifen is an oral, non-steroidal, competitive ER antagonist which has been the first-line endocrine agent of choice for hormone-sensitive metastatic disease. The likelihood of responding to tamoxifen is maximal in those with ER positive disease (60–70%) with a median duration of response of 12–15 months (McGuire, 1978; Mouridsen et al, 1979).

A key problem in advanced breast cancer is that most women (>90%) who respond initially subsequently relapse and develop acquired resistance to tamoxifen, although it is clear that their tumours can remain endocrine-sensitive and respond to

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TABLE 1.
Clinical factors in patients with metastatic breast cancer which may predict response to initial endocrine therapy

Factors predictive for good response to endocrine	Postmenopausal status
	Soft tissue sites of disease (skin, nodes)
	Oestrogen receptor (ER) positive tumour
	Long-disease free interval since primary therapy for early breast cancer
Factors making initial endocrine therapy less appropriate	Symptomatic visceral metastases (e.g. lymphangitis carcinomatosis or progressive liver metastases)
	ER-negative tumour
	Short disease-free interval (12–18 months)
	Relapse on adjuvant tamoxifen (unless ER positive and other good features as above)

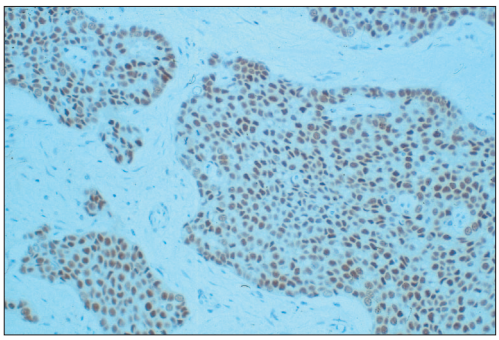


Figure 1. Immunohistochemical assessment of oestrogen receptor expression in breast which can be performed retrospectively on stored fixed paraffin-embedded tissue.

further hormonal interventions (Johnston, 1997). However, an emerging scenario is that most patients have already received tamoxifen in the adjuvant setting and often relapse with metastatic disease while still taking tamoxifen. Effective second-line agents are required.

Previously progestins (megestrol acetate or medroxyprogesterone acetate) were the standard treatment of choice following tamoxifen failure, but recently considerable progress has been made with the development of potent oral aromatase inhibitors which provide maximal oestrogen deprivation in postmenopausal women. The first generation non-steroidal aromatase inhibitor was aminoglutethimide, but its major problem was the lack of specificity for the aromatase enzyme and the fact that it inhibited the adrenal synthesis of both glucocorticoids and mineralocorticoids (which required concomitant use of hydrocortisone).

Within the last 5 years third generation potent oral aromatase inhibitors have entered the clinic, including the non-steroidal inhibitors anastrozole and letrozole, together with the steroidal aromatase inactivator exemestane. These drugs are 2–3 orders of magnitude more potent than aminoglutethimide and are highly selective for the aromatase enzyme without affecting mineralocorticoid or glucocorticoid synthesis.

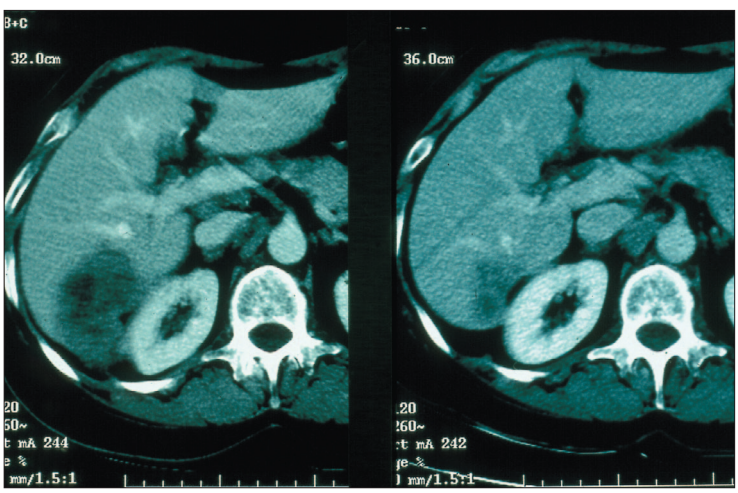
In the metastatic second-line setting, phase III trials have been conducted in over 2000 women comparing each of the third generation aromatase inhibitors with megestrol acetate following failure on tamoxifen (Buzdar et al, 1996a; Dombernowsky et al, 1998; Kaufmann et al, 2000). These have all demonstrated clinical superiority for the third generation aromatase inhibitors over megestrol acetate. An analysis of two randomized phase III trials of 764 patients treated with either anastrozole or megestrol acetate as second-line therapy after tamoxifen failure demonstrated equivalent efficacy in terms of objective response rates (10.3% and 7.9%, respectively) and disease stabilization for 6 months (25.1% and 26.1% respectively), although showed better tolerability for anastrozole (Buzdar et al, 1996a). A subsequent analysis following a median of 31 months follow-up showed a significant improvement in overall survival for anastrozole (hazard ratio 0.78, P=0.02) (Buzdar et al, 1998).

For letrozole, improvements were seen in response rate (hazard ratio 1.82, P=0.04) and time to treatment failure compared with megestrol acetate, although no impact on survival was detected (Dombernowsky et al, 1998). In the recently reported trial with exemestane time to disease progression and overall survival were significantly better than megestrol acetate (Kaufmann et al, 2000).

What is particularly impressive from these trials are the substantial improvements seen in response duration for those who benefited, together with an impact of aromatase inhibitors on overall survival in women who have developed advanced metastatic breast cancer. In the letrozole study the median response duration was >33 months compared with 18 months for megestrol acetate (Dombernowsky et al, 1998), while for anastrozole there was an absolute improvement in 2-year survival from 46.3% to 56.1% with a gain in median survival of 4 months (Buzdar et al, 1998).

Equally impressive are the enhanced response rates seen with aromatase inhibitors in sites of visceral disease, including patients with liver metastases (*Figure 2*). These improvements in clinical endpoints shown for each of the new third generation oral aromatase inhibitors, together with their consistent superior tolerability profile over megestrol acetate (i.e. reduced weight gain and thromboembolic events), have

Figure 2. Response of liver metastases in a postmenopausal patient with advanced breast cancer to aromatase inhibitors. The patient had an original oestrogen receptor-positive cancer and relapsed after 5 years with symptoms of right upper quadrant discomfort.



defined their role as the standard endocrine treatment in advanced breast cancer following tamoxifen failure.

Recently trials have asked whether aromatase inhibitors should challenge tamoxifen as the first-line endocrine agent of choice. The great potential of these studies is to see whether complete oestrogen blockade provided by these drugs provides greater control of hormone-sensitive breast cancer than tamoxifen, thus circumventing the problem of acquired tamoxifen resistance (Johnston, 1997). At this stage published data in one trial with anastrozole compared with tamoxifen as first-line therapy in ER-positive breast cancer showed that anastrozole significantly prolonged the time to disease progression from 5.6 to 11.1 months (P=0.005) (Nabholtz et al, 2000), although in a larger trial no difference was found between the treatments (Bonneterre et al, 2000).

However, in an analysis of patients with ER-positive cancers from both trials, anastrozole significantly prolonged the time to disease progression from 6.4 to 10.7 months (P=0.022) (Buzdar et al, 2000). Likewise preliminary data have shown that letrozole a significantly higher response rate (30% *vs* 20%, P<0.001) and prolonged time to disease progression (median 9 months *vs* 6 months, P<0.0001) than tamoxifen in a prospective randomized first-line endocrine therapy trial in over 900 patients (Mouridsen et al, 2000), while higher response rates were seen with exemestane than tamoxifen in a small pilot study (Paridaeens et al, 2000). It remains to be seen in metastatic disease whether these benefits for aromatase inhibitors will translate into substantial gains in survival over tamoxifen, although these preliminary results suggest that there could be enormous benefit for aromatase inhibitors *vs* tamoxifen in the ongoing adjuvant trials in early breast cancer.

CHEMOTHERAPY

First-line chemotherapy for patients with metastatic breast cancer achieves an objective tumour response in 40–60% patients, with a median response duration of 6–12 months. It is well established that patients who achieve an objective response (complete or partial remission) are more likely to have significant relief of their symptoms with an improvement in their performance status (Baum et al, 1980). A small fraction of patients achieve complete remission which may remain for an extended length of time (Greenberg et al, 1997). While there are no randomized data in metastatic breast cancer of first-line chemotherapy compared with best supportive care to demonstrate the impact of chemotherapy on survival, retrospective studies have shown that chemotherapy is probably associated with a modest 9–12 months gain in survival (Cold et al, 1993).

Anthracyclines

The anthracycline doxorubicin is considered one of the most active cytotoxic drugs in breast cancer, with response rates of 40% when given as a first-line single agent. Anthracycline combinations such as CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) or AC (doxorubicin and cyclophosphamide) are widely used in view of their higher first-line response rates (50–60%) than single-agent therapy. With the increasing use of systemic adjuvant chemotherapy, which in premenopausal patients often involves anthracyclines, more patients will have received combination chemotherapy by the time metastatic disease develops. This may influence the likelihood of response to further treatment (Houston et al, 1993).

An increasing problem is a subgroup of patients with good performance status who have failed an anthracycline-based combination, either as first-line therapy for metastatic disease or having relapsed within a few months of adjuvant chemotherapy, in whom the response rates to further conventional chemotherapy are generally poor (<20–30%) with median durations of response of only 3–6 months (Buzdar et al, 1996b).

Taxanes

New cytotoxic drugs, in particular the taxanes which act against microtubulin structures within the cell, have shown significant efficacy compared with currently available options in patients with relapsed advanced breast cancer (Vermoken and Ten Bokkel Huinick, 1996). Paclitaxel and docetaxel are cytotoxic agents which promote the formation of stable microtubules which then resist depolymerization during cell division. Several randomized phase III trials have looked at the efficacy of these drugs as second-line therapy compared with conventional chemotherapy, especially in those with anthracycline-resistant disease (*Table 2*).

For docetaxel a significantly higher response rate was observed compared with either mitomycin/vinblastine (Nabholtz et al, 1999a) or methotrexate/5-fluorouracil (Sjostrom et al, 1999), with an associated increase in time to progression and in one trial significantly improved overall survival. In a third study superior response rates were seen for docetaxel com-

pared with vinorelbine/5-fluorouracil, although the difference was not significant (Bonneterre et al, 1997).

Paclitaxel has been compared against mitomycin as second-line therapy in a small randomized phase II study (Dieras et al, 1995), while a randomized study of two doses of paclitaxel was performed in patients who had failed prior chemotherapy (Nabholtz et al, 1996) (*Table 2*). On the basis of the randomized clinical trial data to date, the National Institute for Clinical Excellence in the UK recently recommended the use of taxanes as single agent therapy in advanced breast cancer where initial cytotoxic chemotherapy has failed (National Institute for Clinical Excellence, 2000).

In patients with advanced breast cancer who have not received an anthracycline previously, randomized trials have shown superior clinical efficacy for docetaxel compared with doxorubicin (Chan et al, 1999), although this was not seen in two studies for paclitaxel compared with doxorubicin (Sledge et al, 1997; Paridaens et al, 2000a). In untreated patients as first-line chemotherapy paclitaxel was equivalent to conventional cyclophosphamide/methotrexate/5-fluorouracil/prednisolone (CMFP) chemotherapy, although on multivariate analysis improved survival was seen (Bishop et al, 1999).

As taxanes appear to be non-cross resistant with anthracyclines, trials have determined their efficacy and tolerability in combination with anthracyclines as first-line therapy. The results to date have shown equivalence in terms of response rate and progression-free survival both for epirubicin/paclitaxel (ET) *vs* epirubicin/cyclophosphamide (EC) (Luck et al, 2000), and for doxorubicin/paclitaxel (AT) *vs* doxorubicin/cyclophosphamide (AC) (Biganzoli et al, 2000). In contrast, the combination of doxorubicin/docetaxel (AT) *vs* AC was associated with a higher response rate (60% *vs* 46%, P=0.004) and prolonged time to disease progression (median 37 weeks *vs* 32 weeks, P=0.014) (Nabholtz et al, 1999b). Concerns have been raised about whether the haematological and cardiac toxicity is significantly greater with these combinations, and the results of further trials including triple combinations with 5-fluorouracil are awaited.

High-dose chemotherapy

Increasing the dose of conventional chemotherapy regimens up to two-fold has been associated with enhanced response rates, but to date has not

TABLE 2.
Randomized controlled trials of single agent taxanes (docetaxel or paclitaxel) in second-line/anthracycline resistant or first-line metastatic breast cancer

Investigator	Setting	No	Taxane *vs* control	Response rate	Time to progression (weeks)	Overall survival (months)
Nabholtz et al (1999)	2nd line/anthracycline resistance	392	Docetaxel	30.0%*	19*	11.4 *
			MV	11.6%	11	8.7
Sjostrom et al (1999)	2nd line/anthracycline resistance	283	Docetaxel	42%*	27*	10.4
			MF	21%	13	11.1
Bonneterre et al (1997)	2nd line/anthracycline resistance	178	Docetaxel	33%	26	–
			NF	26%	22	–
Dieras et al (1995)	2nd line	81	Paclitaxel	17%*	15*	12.7
			Mitomycin	6%	7	8.4
Nabholtz et al (1996)	2nd line/anthracycline resistance	471	Paclitaxel 175	29%	18*	11.7
			Paclitaxel 135	22%	13	10.5
Chan et al (1999)	1st line/2nd line	326	Docetaxel	47.8%*	26*	15
			Doxorubicin	33.3%	21	14
Sledge et al (1997)	1st line	739	Paclitaxel	33%	26	22.2
			Doxorubicin	34%	27	20.1
			Pac + Dox	46%*	35*	22.4
Paridaens et al (2000)	1st line	331	Paclitaxel	25%	17	15.6
			Doxorubicin	41%*	32*	18.3
Bishop et al (1999)	1st line	209	Paclitaxel	29%	23	17.3*
			CMFP	35%	28	13.9

* P<0.05. CMFP = cyclophosphamide/methotrexate/5-fluorouracil/prednisolone; MF = methotrexate/5-fluorouracil; MV = mitomycin/vinblastine; NF = vinorelbine/5-fluorouracil

impacted on time to progression or overall survival in advanced disease. At the same time it is recognized that inadequate doses of chemotherapy produce an inadequate outcome. Peripheral blood stem-cell harvesting has allowed even higher-dose chemotherapy (i.e. greater than 5-fold increase in dose intensity) to be delivered, with the hope that if response rates could be enhanced yet further by delivery of maximally tolerated dose-intensified chemotherapy, then perhaps survival may be improved. While numerous phase II trials reported on the high response rates which could be achieved with this approach using various drug combinations, patient selection has always been a confounding factor in interpreting the true efficacy of this approach (Rahman et al, 1997). Two large randomized trials have both failed to show any advantage for high-dose chemotherapy compared with conventional dose regimens (Lotz et al, 1999; Stadtmauer et al, 2000).

BISPHOSPHONATES

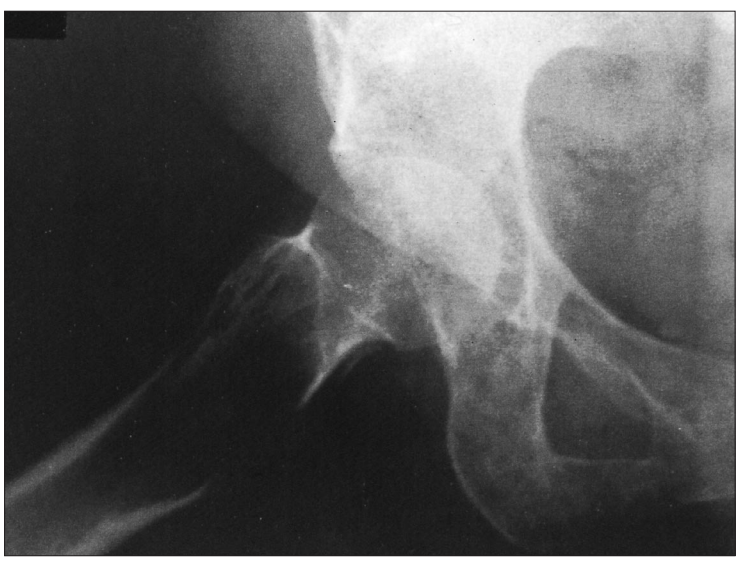
Up to 50% of women who develop metastatic breast cancer present with bone metastases, sometimes as their only site of disease. Many of these patients have indolent disease and as such can survive for many years. Bisphosphonates are bone-specific palliative agents which inhibit tumour-related osteoclast-induced bone resorption associated with breast cancer metastases. In patients with predominantly lytic bone metastases (*Figure 3*), they have been shown to significantly improve quality of life by reducing bone pain and preventing skeletal complications such as fracture, spinal cord compression and hypercalcaemia.

There have been four randomized double-blind placebo-controlled trials in breast cancer patients with bone metastases. Intravenous pamidronate (90 mg as a 2-hour infusion every month for 12 cycles) was compared against placebo infusion in conjunction with chemoendocrine therapy in 382 women with at least one lytic bone lesion (Hortobagyi et al, 1996). The median time to the first skeletal complication was significantly longer in those given pamidronate (13.1 *vs* 7.0 months, P=0.005), and overall fewer patients developed such complications (43% *vs* 56%, P=0.008).

Similar results were seen in 372 patients with advanced breast cancer with lytic bone metastases who were treated with endocrine therapy alone with or without pamidronate, and in a recent combined update of both trials the addition of bisphosphonate therapy was shown to be significantly superior to anticancer therapy alone (endocrine and/or chemotherapy) in preventing skeletal complications and palliating symptoms from bone metastases (Lipton et al, 2000). Similar results have been demonstrated with pamidronate in another trial in 295 patients (Conte et al, 1996). In the final study of 173 patients oral clodronate (1600 mg daily) was compared against placebo tablets (Paterson et al, 1993). There was a significant reduction in the number of hypercalcaemic episodes (28 *vs* 52, P<0.01) and the incidence of vertebral fractures (84 *vs* 124 per 100 patient years, P<0.025). However, in all four studies there was no impact on overall survival.

It is clear that bisphosphonates are a useful and effective palliative treatment for bone disease, and clear guidelines have been issued by the British Association of Surgical Oncologists for their use in women with metastatic breast cancer (Breast Speciality Group, British Association of Surgical Oncologists, 1999). The American Society of Clinical Oncology also released recent guidelines on the use of bisphosphonates (Hillner et al, 2000), stating that this therapy reduces the rate of bone complications (although not mortality) in women with lytic bone disease who may or may not also be receiving systemic therapy (chemotherapy of endocrine therapy). Large randomized trials are in progress in the adjuvant setting to see whether these agents may delay/prevent the development of bone secondaries in women diagnosed with early breast cancer.

Figure 3. Lytic bone metastases in a patient with advanced breast cancer. In addition to specific oncological treatment such as radiotherapy and endocrine/chemotherapy, plus in this case orthopaedic pinning of the femur to prevent fracture, bisphosphonate therapy has a role in significantly improving bone pain, and delaying further progression of disease within the bone.



FUTURE THERAPIES

The major limitation of conventional endocrine and chemotherapy in metastatic disease is that most tumours become resistant. Biological therapies offer a novel approach which may circumvent drug resistance, although the greater opportunity lies in the setting of minimal residual disease where trials are being proposed of maintenance therapy following chemotherapy-induced remission in order to prolong time to disease progression.

One of the more promising approaches includes immunotherapy strategies and drugs which target aberrant growth factor or signal transduction pathways. While breast carcinomas have never been considered immunogenic, certain surface antigens such as the MUCl glycoprotein are aberrantly glycosylated in breast cancer. Synthetic peptides have been generated which can induce a specific immune response when coupled with a carrier protein and an immunological adjuvant (Miles et al, 1996), and a worldwide randomized phase III study in patients with metastatic breast cancer following response to chemotherapy is in progress.

Recently, there has been considerable interest concerning the role of trastuzumab (Herceptin), a humanized monoclonal antibody directed against the cell surface growth factor receptor c-erbB2 (also known as HER-2) which is overexpressed in 25–30% of breast cancers (Slamon et al, 2001). Such tumours are thought to be resistant to both endocrine and conventional chemotherapies, and trastuzumab either given alone or in conjunction with conventional therapy offers an opportunity to modulate aberrant growth factor activity in patients with resistant disease. In patients with HER-2-positive tumours trastuzumab administered as a weekly intravenous infusion produced response rates of up to 35% as first-line therapy for metastatic breast cancer (Vogel et al, 2000). In a randomized phase III trial in 469 women with HER-2-positive metastatic breast cancer (Slamon et al, 1998), the addition of trastuzumab to taxane or anthracycline-based chemotherapy significantly enhanced both response rates (62% *vs* 36%) and time to disease progression (8.6 *vs* 5.5 months). As such, this represents this first example of a targeted biological therapy for advanced breast cancer successfully entering the clinic, and other novel drugs are in development which target various components of the internal signal transduction pathway.

KEY POINTS

- Taxanes are now indicated for patients who have failed previous anthracycline-based chemotherapy.
- Third generation aromatase inhibitors are the standard of care after tamoxifen in oestrogen receptor-positive postmenopausal breast cancer.
- Current trials indicate that aromatase inhibitors may be superior to tamoxifen.
- Bisphosphonates significantly reduce morbidity from bone metastases and may delay progression of disease within bone.
- Biological therapies may herald a new era of systemic treatment options for metastatic breast cancer.

CONCLUSIONS

The key recent advances in metastatic breast cancer have been the introduction of potent aromatase inhibitors as endocrine therapy after tamoxifen failure, the taxanes which may show activity in anthracycline resistant disease, and bisphosphonates for the specific management of metastatic bone disease. Clinical trials with each of these agents have demonstrated significant improvements in various clinical endpoints in comparison with previous standards of care, and as such these therapies are likely to make a major impact on the treatment and quality of life for such patients. While current trials are investigating the role for these new drugs either in first-line therapy or the adjuvant setting, the persisting problem remains the development of resistance manifest as subsequent relapse.

There is great expectation that the next generation of trials with new biological agents, used either alone or in conjunction with conventional therapies, could have a similar impact on future treatment options, giving renewed hope to the thousands of women who continue to develop metastatic breast cancer. HM

Conflict of interest: none.

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