Medical Management of Breast Cancer

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Chapter 18

New agents

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Introduction

Despite significant advances in the management of breast cancer over the last few decades, there is still no curative treatment for patients with advanced disease (Henderson, 1987).

It is therefore very important that active and preferably less toxic new treatments against breast cancer are discovered. In order to achieve this aim, several research avenues are being pursued, including the following:

1. The discovery of active compounds through standard screening methods and/or through the design of new models for drug screening.
2. The development of analogues of known active drugs, with increased antitumour activity and/or fewer side-effects.
3. The evaluation of new strategies to enhance the efficacy of known drugs, including dose intensity, alternating chemotherapy, biochemical modulation and the reversal of drug resistance.
4. The study of the biological behaviour of breast cancer cells and the therapeutic use of biological response modifiers, such as monoclonal antibodies, growth factors or cytokines.

5. The development of new agents aimed at improving quality of life and/or reducing morbidity of breast cancer (Table 18.1).

In this chapter, a brief overview of these strategies for anticancer drug development will be presented. (New endocrine therapies including aromatase inhibitors, antioestrogens and LHRH analogues are discussed in Chapters 6–11 and diphosphonates to control hypercalcaemia and bone metastases in Chapter 33.)

New drugs

The testing of new chemical structures should be a priority in anticancer drug development. Until now the majority of compounds which have been screened for antitumour activity were either analogues of known drugs or compounds structurally related to drugs already studied in the past. During the last few years, many new agents have been evaluated in disease-oriented phase II trials. However, only a few of them have shown significant activity in patients with advanced breast cancer.
Table 18.1 Strategies for anticancer drug development in breast cancer

- The discovery of new active drugs
- The development of analogues with improved therapeutic index
- The testing of new concepts to increase the efficacy of known drugs
- The study of biomodulators and drug targeting
- The evaluation of agents which reduce disease morbidity

In 113 such patients was only 9 per cent and remissions were generally of very brief duration (Sledge and Roth, 1989). Three more recent phase II studies using higher doses of up to 120 mg/m² every 4 weeks as first-line therapy report an overall response rate of around 50 per cent (Sledge and Roth, 1989). Again median response duration was only 4 months, but these studies nevertheless suggest that cisplatin as first-line treatment is a very active drug in metastatic breast cancer. However, this is a toxic therapy and its long-term role in this disease still needs to be established (see also Chapter 14).

Carboplatin

Carboplatin is an analogue of cisplatin without the nephrotoxicity or neurotoxicity of the parent compound. It is generally much better tolerated than cisplatin and, in particular, causes less nausea and vomiting. It already has an established role in the treatment of ovarian carcinoma and small cell lung cancer. So far it has mainly been studied only in heavily pretreated patients where it has not shown activity (Booth et al, 1985). It has also been used as first-line, single-agent therapy in a standard dose of 400 mg/m²; here again only relatively low activity was seen with a 20 per cent objective response rate (Kolaric and Vukas, 1990). This is disappointing; in other tumour types carboplatin is as active as cisplatin, and its relatively low toxicity profile would make it a very attractive drug in breast cancer. Carboplatin is also being investigated in higher dosage (800 mg/m²) in combination with high-dose cyclophosphamide and thiopeta with autologous bone marrow rescue (Eder et al, 1990); results are too preliminary to draw any firm conclusions. There is an argument for assessing carboplatin further.

Mitozantrone

Mitozantrone is one of the most active new cytotoxic agents to be discovered against breast cancer in the 1980s, and is now widely marketed throughout the world. It is an anthracenedione derivative, with a similar ring structure to the anthracyclines (Figure 18.1) and appears to cause cytotoxic effects through the induction of topoisomerase II-mediated DNA damage (Allagra et al, 1985)—details given in Chapter 14.

Platinum compounds

Cisplatin

Cisplatin and other platinum analogues have been studied in phase II trials in patients with breast cancer. Initial results with cisplatin were disappointing, but usually included heavily pretreated patients (Hartmann and Loprinzi, 1988). The overall response
cisplatin derivative initially thought to have less nephrotoxicity than the parent compound. It has been assessed in three phase II studies in doses of 225–300 mg/m² every 3–4 weeks. Overall, only 7 responses (8 per cent) have been seen in 89 pretreated patients (Hortobagyi et al, 1987; Casper et al, 1988; Meisner et al, 1989), although one patient had complete regression of pulmonary nodules lasting more than 18 months. Myelosuppression was dose limiting but nausea, vomiting and diarrhoea, and general malaise were also important side-effects. Iproplatin has not found a role in the treatment of breast cancer or other malignancies.

**Anthrapyrazole CI941**

CI941 is one of a number of anthrapyrazole compounds synthesized in an attempt to produce a drug at least as active as doxorubicin (Adriamycin) but lacking its major toxicities including cardiotoxicity. It has a structure very similar to mitozantrone (see Figure 18.1). In experimental tumour studies, it has a wide spectrum of activity and probably acts as a topoisomerase II inhibitor.

In a phase II study recently carried out in the Royal Marsden Hospital, London anthrapyrazole CI941 has shown a very high level of clinical activity. Thirty patients with advanced breast cancer have so far been treated with CI941 in a dose of 50 mg/m² by intravenous bolus injection every 21 days. Ten of these patients had received previous chemotherapy but not an anthracycline. Eighteen patients (60 per cent) have achieved an objective tumour response including 5 out of 8 (62 per cent) patients previously treated with CMF (cyclophosphamide, methotrexate and 5-fluorouracil). Leucopenia was the most significant toxicity. Mild alopecia occurred in most patients, but severe alopecia requiring a wig occurred in only 22 per cent of patients. Nausea and vomiting were mild (Smith IJ, 1990, personal communication).

These results suggest that this new agent is one of the most promising yet discovered against breast cancer and that it may be less toxic than doxorubicin (Adriamycin). Further studies are under way.

**Elliptinium**

Elliptinium acetate is a synthetic derivative of the indole plant alkaloid ellipticine, and it appears to act as a DNA-intercalating agent and to cause the inhibition of topoisomerase II. It leads to objective tumour responses in about 25 per cent of patients. It lacks significant bone marrow toxicity, but causes moderate nausea and vomiting and, in some cases, acute haemolysis (Rouesse et al, 1985). Because of these side-effects, the drug has failed to acquire a place among the conventional cytotoxic agents against breast cancer.
Peptichemio

Peptichemio is a mixture of synthetic peptides containing \( m\)-[di-(2-chloroethyl)-amino]-L-phenylalanine with amino acids. The peptide nature of this mixture of compounds may entail novel mechanisms of transport or detoxification, which might be relevant to its potential activity (Fornasiero et al., 1986). It achieves around a 20 per cent objective response rate in patients with advanced breast cancer.

Lonidamine

Lonidamine is a substituted indazole carboxylic acid initially studied for its antispermagenic properties. Somewhat unexpectedly it was found to have moderate anticancer activity in experimental tumour systems. Its mechanism of action here is not entirely clear but in vitro studies show that lonidamine inhibits oxygen consumption and aerobic glycolysis with marked ultrastructural mitochondrial changes. It has no myelosuppressive or other typical toxicities associated with anticancer agents, but it does cause myalgia which is usually transient.

Lonidamine has already shown modest activity in advanced breast cancer. In a Canadian study, 5 out of 30 patients (17 per cent) achieved a partial response (Band et al., 1986); in an Italian study 16 per cent of 25 evaluable patients achieved a response (Ponzato et al., 1989), and in a recent UK study carried out at the Royal Marsden Hospital 3/28 patients (11 per cent) achieved a partial response and three others (11 per cent) a minor response.

It is unlikely that lonidamine will have a major role as single agent treatment, but in vitro studies suggest that it may inhibit recovery from potentially lethal damage from radiotherapy and cytotoxic drugs. It is therefore currently being investigated as a potentiator of both radiotherapy and combination chemotherapy in randomized trials. In an ongoing Italian trial, the addition of lonidamine to conventional FAC (5-fluorouracil, doxorubicin (Adriamycin), cyclophosphamide) chemotherapy has so far achieved a significantly increased response rate (63 per cent vs 44 per cent), and prolonged median time to disease progression (40 weeks vs 25 weeks) (Calabresi et al., 1990).

Dibromodulcitol

Dibromodulcitol (mitolactol) is a cytotoxic brominated hexitol which achieves objective responses in about 20 per cent of patients with advanced breast cancer. It has been administered orally and its major side-effects are myelosuppression and nausea and vomiting (Creech et al., 1984).

Taxol

Taxol is a plant product derived from the western yew tree which exerts its cytotoxic effects by interfering with microtubule structure and function. Preliminary data from phase II trials of this compound in patients with advanced breast cancer have shown significant antitumoural effects (Grever M., personal communication). However, the role of taxol in the management of patients with breast cancer should await the results of further clinical trials.

Analogues of known drugs

Anthracycline analogues

Over the last few years, several anthracycline analogues of doxorubicin (Adriamycin) have been developed aimed at identifying compounds with at least comparable antitumour activity, but less toxicity than the parent compound. Epirubicin, pirarubicin, and idarubicin are examples.
Epirubicin

Epirubicin (4'-epidoxorubicin) is an anthracycline analogue which differs from doxorubicin in the epimerization of the hydroxyl group in the 4' position of the amino sugar daunosamine. It has been shown to be as active as doxorubicin in patients with advanced breast cancer at comparable doses, whilst appearing to be less cardiotoxic and also less myelosuppressive (Henderson et al, 1987). Epirubicin is now being extensively studied in combination chemotherapy regimens (see also Chapter 14).

Pirarubicin

Pirarubicin (4-O-tetrahydropranyl-doxorubicin) has shown objective antitumour activity (about 30 per cent) in breast cancer during phase II evaluation (Samonigg et al, 1989). Its toxicity profile seems to be similar to that of doxorubicin.

Idarubicin

Idarubicin (4-demethoxy-daunorubicin) is an anthracycline analogue in which the methoxyl group from the aglycone was substituted with hydrogen (Lionetto et al, 1986). It seems to be as effective as doxorubicin against breast cancer, but less cardiotoxic. The main potential advantage of idarubicin in relation to other anthracycline analogues rests on its high bioavailability, making it suitable for an oral formulation. It is tolerated extremely well as a single agent in elderly patients.

Vinca alkaloid analogues

Vindesine

Vindesine (desacetylvinblastine) is a vinca alkaloid analogue which causes myelosuppression but less neurotoxicity than vincristine. It was shown to produce objective tumour responses in about 20 per cent of patients during phase II trials in advanced breast cancer (Schwartsmann and Bender, 1988).

Navelbine

Navelbine (5'-nor-anhydrovinblastine) is a semi-synthetic vinca alkaloid with broad experimental antitumour activity both in vitro and in vivo. Clinical phase II studies in advanced breast cancer have suggested much higher activity than with vincristine, vinblastine and vindesine; response rates of 30–40 per cent have been reported in four studies involving over 250 patients in France and Italy (Boccardo et al, 1989; Fumoleau et al, 1990). Leucopenia is dose limiting; but otherwise the drug is well tolerated with a low incidence of severe alopecia, neuropathy, nausea and vomiting. An oral preparation has also been developed but formulation problems still exist.

Biochemical modulation of known antitumour agents

5-Fluorouracil

5-Fluorouracil is frequently included in drug combinations for both advanced breast cancer and adjuvant treatment (Tormey et al, 1982; Henderson et al, 1987). The antitumour effects of this drug are mainly due to the inhibition of pyrimidine synthesis which is accomplished by the inhibition of the enzyme thymidylate synthase (TS) (Pinedo and Peters, 1988).

Recently, it has been demonstrated that by providing an extra source of reduced folates (eg, folinic acid), the binding of 5-fluorouracil to TS is enhanced. In vitro and animal studies have demonstrated an increased antitumour activity for the 5-fluorouracil/folinic acid combination (Allegra et al, 1987). Clinical studies exploring the biochemical modulation of 5-fluorouracil by folinic acid have
reported objective responses in around 30 per cent of patients. This combination has also demonstrated antitumour activity in patients initially failing to respond to 5-fluorouracil-containing regimens (Marini et al, 1987). This approach deserves further evaluation both as part of drug combinations in the management of advanced disease and in the adjuvant setting.

Studies on the reversal of drug resistance

Recently, the phenotype of multidrug resistance has been identified as a distinct biological entity. A key discovery in its understanding was the identification of a cell membrane glycoprotein (P-170), which appears to act as a drug carrier, mediating the efflux of a broad class of agents, including in particular natural products (Dalton et al, 1989a).

It has been demonstrated that several agents, including calcium channel blockers and calmodulin inhibitors, are able to circumvent this efflux mechanism, reversing this type of drug resistance in experimental models (Dalton et al, 1989b). Over the last few years, several studies have been performed to test the ability of calcium channel blockers to overcome drug resistance in the clinic. Initial results in patients with haematological malignancies were encouraging, but clinical trials utilizing agents, such as verapamil, have been hampered by the risk of cardiotoxicity.

Currently, several trials are evaluating the role of calcium channel blockers in overcoming drug resistance in patients with refractory breast cancer. The outcome of these studies will be available during the next few years. However, preliminary results suggest that P-glycoprotein-dependent multidrug resistance is uncommon in breast cancer, and other mechanisms, including changes in topoisomerase activity or increased intracellular levels of detoxification enzymes, are more common. In the authors’ laboratory, ongoing studies which focus on the intracellular distribution of anthracyclines in resistant tumour cells suggest that differences in the nuclear/cytoplasm ratio of drug concentrations could be an alternative explanation for the phenotype of non-P-glycoprotein-dependent drug resistance.

Biomodulators

Over the last decade, important advances in the biology of breast cancer have been made. With developments in molecular biology, genetic engineering and basic immunology, more selective and biologically orientated forms of anticancer therapy have become available. Preclinical and clinical studies are under way, exploring the use of monoclonal antibodies, oncogene products, growth factors and cytokines.

Monoclonal antibodies

Monoclonal antibodies raised against membrane targets in human breast cancer cells are under development, initially for tumour imaging and perhaps in the future for therapeutic purposes. The antibodies L1CR-LON-M3 and L1CR-LON-M8 are examples (Foster and Munro-Neville, 1984). More recently, the radiolabelled antibody 171A-F(ab')2 was studied in both breast and colorectal cancer patients, and showed some localization at tumour sites (Fairweather et al, 1982). However, it is too early to draw any conclusions regarding the potential role of this approach in the clinical management of breast cancer patients (Schlom, 1986; Pimm, 1987).

Cytokines

Cytokines are a group of proteins and glycoproteins
secreted by cells of the immune system with specific regulatory effects on other cell types. Currently, there is a great deal of interest in their potential use as anticancer agents through mediation of the immunological response to cancer cells. They include the interferons and interleukin 2 (IL-2).

Interferons have been shown to induce the expression of oestrogen receptors in oestrogen receptor (ER)-negative breast cancer cells in vitro suggesting that they might enhance or restore hormone responsiveness in breast cancer cells; the effect may also involve interaction with the transforming growth factor TGFβ (Dimitrov et al, 1984; Fisher and Grant, 1985). α-Interferon has been assessed clinically in the management of metastatic breast carcinoma but the overall response rate in cumulative data is only 11 per cent, with most responses coming from just two studies (Goldstein and Laslow, 1986). Response rates to β-interferon are even lower, although fewer patients have been treated with these agents and studies are still in progress.

The treatment of breast cancer with interleukin 2 (IL-2), with or without the administration of lymphocyte-activated killer (LAK) cells, has been disappointing. Ninety-one patients have so far been reported as being treated with IL-2 and only three have achieved a partial response (Rosenberg et al, 1989; Gore ME, 1990, personal communication).

Tamoxifen itself may exert its effects in breast cancer cells, not only via binding to oestrogen receptors but also as a biological response modifier. It has recently been demonstrated that patients receiving tamoxifen showed a significant increase in NK (natural killer) cell activity within a month of starting treatment, with NK cell activity returning to basal levels when treatment was stopped (Berry et al, 1987).

It is becoming clear that the dose and schedule in cytokine therapy are extremely important and future research will concern the development of more rationally designed treatments based on our knowledge of complex interactions between cytokines and cell mediators; these could include, for example, combinations of interferons and IL-2, and combinations of cytokines with chemotherapy.

Design of new methodologies for drug development

New screening methods

In order to avoid the large number of negative phase II studies with new compounds in patients with solid tumours such as breast cancer, it is urgent that screening systems are developed which simulate more adequately the clinical situation (Schwartzman et al, 1988).

Currently, the National Cancer Institute (USA) is evaluating an in vitro screening method whereby new compounds are tested in various panels of human tumour cell lines in a disease-oriented fashion. Using this approach, it is expected that compounds exhibiting antitumour activity against certain solid tumour types are selected instead of compounds exhibiting non-specific cytotoxicity (Boyd and Chabner, 1989). Presently, two human breast cancer cell lines are included in the panel, i.e., MCF-7 and MCF-7/ADR (resistant to doxorubicin).

In the European Organisation for Research into the Treatment of Cancer (EORTC), the value of human tumour xenografts as a model for preclinical phase II studies is under evaluation as part of a multicentre study. The validity of this model is being tested in the following ways: by determining the antitumour activity of both clinically active and inactive drugs in each tumour type included in the panel; by comparing the antitumour profile of each drug in different human tumour xenografts with that observed in the patients; and also by assessing whether the human tumour cell lines included in the panel simulate the clinical situation adequately (Boven et al, 1988). Presently, four tumour cell lines are available in the panel: MAXF 401, MAXF 449, MAXF 583 and MAFX 857.

Methodology of clinical phase II trials

Phase II trials in patients with advanced breast cancer are limited by the fact that most patients participating in these studies have progressive metastatic
disease despite treatment with established chemotherapy regimens. These chemotherapy-resistant patients are not an ideal population for testing new drugs. Therefore, it would be preferable to test promising new compounds in selected subgroups of patients as first-line therapy and/or at an earlier stage.

Ahmann et al. (1987) have investigated the feasibility of this approach by testing new drugs in chemotherapy-naive patients in randomized trials comparing standard combinations with single-agent investigational therapy. In this trial design, patients can be crossed-over from the experimental arm to standard therapy after an initial evaluation of response. A review of three consecutive trials showed that patients randomized initially to new drug therapy did not have any significantly reduced survival, although no clear stratification was made between patients with aggressive vs indolent disease (Hayes and Henderson, 1987). This approach is gaining more attention and may be applied more widely in future.

References


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