REGIONAL DRUG AND THERAPEUTICS CENTRE

(NEWCASTLE)

THE USE OF LIPOSOMAL DOXORUBICIN (MYOCET®▼) IN THE MANAGEMENT OF METASTATIC BREAST CANCER

Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH

October 2008

REGIONAL DRUG AND THERAPEUTICS CENTRE

(NEWCASTLE)

THE USE OF LIPOSOMAL DOXORUBICIN (MYOCET®▼) IN THE MANAGEMENT OF METASTATIC BREAST CANCER

Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH

October 2008

ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	*Date issued*
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer	September 2007
The use of entecavir in the management of chronic hepatitis B infection	March 2007
The use of natalizumab in the management of multiple sclerosis	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer **(N)**	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer **(N)**	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004

Older reports are available via our website or on request

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

Regional Drug and Therapeutics Centre
Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH
Telephone 0191 232 1525 / Fax 0191 260 6192
e-mail: nyrdtc.di@ncl.ac.uk
Web site: www.nyrdtc.nhs.uk

CONTENTS

SUMMARY

- **Breast cancer is the most common malignancy in females in England and is the most common cause of cancer mortality in women. Anthracycline cytotoxic antibiotics such as doxorubicin and epirubicin have been used for many years and they play an important role in chemotherapy regimens used for breast cancer but they are limited by cardiotoxicity. Myocet®▼ is a specific formulation of doxorubicin that is encapsulated within liposomes, designed to reduce cardiotoxic effects.**
- **Myocet®▼, in combination with cyclophosphamide, is licensed for the first-line treatment of metastatic breast cancer in women.**
- **Myocet®▼ has been evaluated in three phase III studies in breast cancer, with comparisons against standard doxorubicin and epirubicin. In comparisons with standard doxorubicin the primary outcome was the incidence of cardiotoxicity, with Myocet®▼ demonstrating less cardiotoxicity with no loss of efficacy. In comparison with equal doses of epirubicin, Myocet®▼ was as effective with no significant difference in cardiotoxicity.**
- **Compared with standard doxorubicin Myocet®▼ did not present any additional safety issues other than a reduced incidence of cardiotoxicity. Compared with equal-dose epirubicin, Myocet®▼ was not associated with increased incidences of neutropenia and stomatitis/mucositis and a reduced incidence of injection site toxicity.**
- **Myocet®▼ is a significant advance on standard doxorubicin and at a lower cost than the only alternative liposome-encapsulated doxorubicin formulation, Caelyx®▼. It is, however, substantially more expensive than standard doxorubicin. The available evidence for the efficacy of Myocet®▼ does not permit a robust assessment of its place in therapy, but merely confirms its advantages over standard doxorubicin.**
- **Myocet®▼ may be a useful option for achieving cumulative doxorubicin doses greater than the currently recommended maximum in patients who are sufficiently medically fit to withstand prolonged treatment with an anthracycline. However at present there is insufficient evidence for proper assessment of Myocet®▼ and due to the comparatively high cost of treatment its widespread use is currently not recommended.**
- **Myocet®▼ is one of many strategies that can be used to reduce the cardiotoxic effects of doxorubicin. Others include the use of epirubicin, dexrazoxane, and use of an alternative liposomal formulation of doxorubicin (Caelyx®▼). Myocet®▼ is about 50 to 60 times the cost of standard doxorubicin, or about 8 to 11 times the cost of epirubicin, but costs less than Caelyx®▼.**

BACKGROUND

In England breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women. [1] In 2004 there were 36,939 new cases of female breast cancer registered in England, representing a crude incidence rate of 145 per 100,000 of the female population. [1] Mortality from breast cancer in the UK has fallen dramatically since the introduction of the national breast screening programme for women aged between 50 and 70 years. [2,3] In the period 1989 to 2005 the age-standardised death rate for female breast cancer fell by 33%. Around 10,300 women died from breast cancer in England in 2006, a rate of 40 deaths per 100,000 women. [2] Earlier detection and improved treatment have meant that survival rates have risen. The five-year survival rate among the 170,700 women diagnosed with breast cancer during 1999-2003 was 81%. [4]

Approximately 10% of patients in England present with advanced disease with distant metastases at the time of first diagnosis (~3,690 women per year). In addition, around 50% of women diagnosed in England with early or localized breast cancer will eventually relapse and develop metastatic disease (~18,470 women). The risk of developing metastatic disease relates to known prognostic factors, including oestrogen-receptor negative status, primary tumour greater than 3 cm and axillary node involvement. [5]

Alongside surgical advances, chemotherapy is an important aspect in the treatment of breast cancer. The actual drugs and combinations used will vary depending on many factors, for example whether pre- or post-surgery, advanced or early-stage disease, or whether the tumour is hormone-sensitive. Anthracycline cytotoxic antibiotics such as doxorubicin and epirubicin have been used for many years in the treatment of numerous malignancies and they play an important role in regimens used for breast cancer. Evidence from several studies has demonstrated survival improvements of around 4 to 5% with anthracycline regimens over treatment with cyclophosphamide, methotrexate, and fluorouracil, and these are now increasingly used as standard in UK centres. More novel regimens include the use of anthracyclines in combination with, or sequential to, taxane cytotoxic drugs (i.e. docetaxel and paclitaxel). [6,7]

Doxorubicin is an anthracycline antibiotic with complex cytotoxic mechanisms involving intercalation between deoxyribonucleic acid (DNA) base pairs. As a consequence, doxorubicin interferes with DNA strand separation and inhibits helicase, DNA topoisomoerase II and DNA and RNA polymerase activities. This results in the inhibition of DNA replication and transcription, as well as induction of DNA fragmentation. Doxorubicin exerts additional cytotoxic effects mediated by inhibition of cytochrome c oxidase activity, free radical formation and lipid peroxidation, producing direct membrane effects, and chelation of iron and generation of reactive oxygen species, resulting in oxidative stress. Doxorubicin may also affect a caspase-dependent pathway when inducing apoptosis. [8]

Doxorubicin is widely used in a range of solid and haematological malignancies but cardiotoxicity limits its use. The cardiotoxicity associated with doxorubicin, and anthracyclines in general, was noticed early in their development and can be divided into acute, subacute and late forms. [9] The acute form usually presents within 24 hours and can be managed with supportive therapy. There is no additional morbidity and no association with subsequent chronic toxicity. Subacute toxicity typically presents four to eight weeks after initial exposure, but can present up to 30 months

after the last dose. It is characterised by myocyte loss and cellular changes resulting in clinical signs of dyspnoea, tachycardia and biventricular failure. Late-onset cardiomyopathy can occur between four and 20 years after treatment, presenting as late clinical decompensation following subacute symptoms, or as cardiac failure in those with no previous symptoms. In adult patients late-onset cardiomyopathy can be difficult to distinguish from underlying pathology in an ageing population. [9]

The mechanism of anthracycline cardiac toxicity is not fully known and several mechanisms have been proposed including: [9]

- Damage to mitochondrial DNA
- Generation of free radical molecules
- Interference with myocardial energy metabolism

There are several risk factors associated with the pathogenesis of anthracycline-related cardiomyopathy, including: [9]

- Prior or concurrent radiotherapy
- Age > 65 or < 4 years
- Pre-existing cardiac disease or hypertension
- Previous cyclophosphamide exposure

Perhaps the most important and the most easily modifiable risk factor is the cumulative life-time dose of anthracycline. In the case of doxorubicin, life-time cumulative doses are limited to a maximum of 450 to 500 mg per square metre of body surface area (m^2 BSA). [9-11] Cumulative doses above 500 mg/m^2 BSA are associated with a substantial increase in cardiac toxicity. [9,11]

Several strategies exist with the aim of countering the cardiotoxic effects of doxorubicin whilst maintaining cytotoxic efficacy. Epirubicin is an anthracycline analogue of doxorubicin which, at equivalent doses, demonstrates similar efficacy with reduced cardiotoxicity. This enables greater life-time cumulative doses of anthracycline, generally about 900 mg/m^2 BSA, with associated increases in survival. [9-12]

Dexrazoxane is an analogue of ethylene diamine tetra-acetic acid (EDTA) and is thought to exert cardioprotective effects by chelating ferric ions thus arresting the further formation of reactive radicals. It is administered as an intravenous infusion prior to administration of doxorubicin at a dose equal to 20 times the dose of doxorubicin. [11,13]

Another technique that has been applied is the encapsulation of doxorubicin molecules within liposomes. [9-12] This is thought to reduce exposure of myocardial tissue and increase exposure of malignant tissue to doxorubicin. [11,12,14] There are two commercially available liposomal formulations of doxorubicin which differ in the nature of the lipid component:

Caelyx®▼ (Schering-Plough) is a liposomal presentation of doxorubicin with polyethyene glycol embedded in the lipid layers. [12,15]

Myocet®▼ (Cephalon) is a proprietary form of doxorubicin that, once prepared, is encapsulated within phospholipid liposomes. Its pharmacokinetics demonstrates a high degree of inter-patient variability. Generally, compared to standard doxorubicin at the same dose, plasma levels of total doxorubicin are higher with Myocet®▼ while the peak plasma levels of free doxorubicin (i.e. non-liposome encapsulated) are lower. [16]

Myocet®▼, in combination with cyclophosphamide, is licensed for the first-line treatment of metastatic breast cancer in women. [16] The purpose of this report is to review the efficacy of Myocet®▼ with respect to its licensed indication and consider its place in treatment.

EFFICACY

In the treatment of metastatic breast cancer Myocet®▼ has been evaluated in three, published, phase III active-comparator, randomised controlled trials.

Harris et al randomised 224 patients with metastatic breast cancer to first-line treatment with Myocet®▼ (n = 108) or standard doxorubicin (n = 116), with the primary outcome focusing on response rate. [17] Patients had a median age of 58 years (range 26 to 85) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (i.e. otherwise in reasonable health). Baseline characteristics were well balanced except for progesterone receptor status (33% vs. 50% respectively, p = 0.02). For inclusion in the study patients were required to have a left ventricular ejection fraction (LVEF) ≥ 50%. Patients were ineligible if they had received a cumulative lifetime doxorubicin dose of > 300 mg/m^2 BSA, or if they had received any cytotoxic chemotherapy for metastatic disease or adjuvant chemotherapy within the previous six months. Other exclusion criteria were a history of congestive heart failure (CHF), serious cardiac arrhythmia, or myocardial infarction within the previous six months. Treatment was commenced with Myocet®▼ or doxorubicin at 75 mg/m^2 BSA, over one hour, once every three weeks. Granulocyte-colony stimulating factor (GCSF) was also used. The regimen was to be interrupted if patients did not meet specific haematological parameters, and similarly dose adjustments in 15 mg/m^2 BSA increments were also stipulated depending on haematological parameters and other toxicities. After a median of four cycles of treatment and median cumulative doses of 360 mg/m^2 BSA (range 75 to 1110) and 390 mg/m^2 BSA (range 75 to 840) of Myocet®▼ and doxorubicin respectively there was a significant benefit in terms of discontinuation due to cardiac events. Twenty-nine per cent of the doxorubicin group compared to 13% in the Myocet®▼ group discontinued treatment due to a cardiac event (p = 0.0001, defined as a decrease in resting LVEF by ≥ 20 points from baseline to a final value ≥ 50%, or a decrease of ≥ 10 points from baseline to a final value of < 50%, a cardiac biopsy of grade ≥ 2.5, or clinical evidence of CHF). There were no significant differences in any other parameter of efficacy or toxicity.

Batist et al randomised 142 patients with metastatic breast cancer to treatment with Myocet®▼ and cylophosphamide, and 155 patients to treatment with standard doxorubicin and cyclophosphamide. [18] Patients were aged between 22 and 88 years and were otherwise in reasonable health (ECOG status ≤ 2). Patients were required to have a LVEF ≥ 50% and no history of CHF, arrhythmia, or myocardial infarction within 6 months. Patients were eligible if they had received prior adjuvant chemotherapy > 6 months previously and the cumulative dose of doxorubicin did not exceed 300 mg/m^2 BSA. Treatment was initiated at a dose of 60 mg/m^2 BSA over one hour for Myocet®▼ and doxorubicin, and 600 mg/m^2 BSA over 15 minutes for cyclophosphamide, using three-weekly cycles. Dose reductions were allowed depending on tolerability and haematological toxicity and GCSF was available as indicated. The primary outcome measure was the rate of cardiotoxicity, defined as a decrease in LVEF ≥ 20 points from baseline to a final value of ≥ 50% or a decrease

of ≥ 10 points to a final value of < 50% or clinical evidence of CHF. The primary efficacy measures were the complete response (CR) and partial response (PR) rates, defined as absence of disease ≥ 6 weeks, or ≥ 50% reduction in tumour size ≥ 6 weeks with no disease progression, respectively. Other measures included the duration of response, overall survival, time to disease progression (TTP), and time to treatment failure (TTF, defined as discontinuation due to adverse events, lack of efficacy, intolerance, cardiac toxicity, disease progression, or death). After a median follow-up of 20 months 6% of patients treated with Myocet®▼ and 21% treated with doxorubicin exhibited protocol-defined cardiotoxicity (p = 0.0001). The CR plus PR rate was 43% in both groups. Other measures demonstrated non-significant differences in favour of Myocet®▼: median duration of response (9.6 vs. 9.1 months, p = 0.38), median overall survival (19 vs. 16 months, p = 0.79), median TTP (5.1 vs. 5.5 months, p = 0.82), and median TTF (4.6 vs. 4.4 months, p = 0.30).

A combined retrospective analysis of patients who had prior exposure to doxorubicin in the phase III studies by Harris [17] and Batist [18] (combined n = 68) found that most outcome measures were significantly better for patients treated with Myocet®▼ compared to those treated with doxorubicin. The exceptions were the median time to progression and overall survival, which demonstrated no significant difference. The most striking result was an increased objective response (CR+PR) rate of 31% vs. 11% (p = 0.04). [19]

Chan et al conducted a randomised comparative trial of Myocet®▼ (n = 80) or epirubicin (n = 80), plus cyclophosphamide, as first line treatment in patients with metastatic breast cancer. [20] The median age of patients was 54 years (range 19 to 82), and most were otherwise in reasonable health (ECOG status ≤ 2). Patients were eligible if they had not previously been exposed to any anthracycline and they were required to have a resting LVEF ≥ 50%. Patients were excluded if they had received prior adjuvant chemotherapy, radiotherapy, or chemotherapy for metastatic disease, or had a history of cardiac problems. Myocet®▼ and epirubicin were administered at equal doses of 75 mg/m^2 BSA over one hour, plus cyclophosphamide 600 mg/m^2 BSA over 15 minutes. Treatment was repeated once every three weeks to a maximum of eight cycles. GCSF was permitted if haematological measures indicated. Dose reductions were permitted in 15 mg/m^2 BSA steps for Myocet®▼ and epirubicin, and 150 mg/m^2 BSA steps for cyclophosphamide, depending on haematological parameters and treatment-related toxicities. The primary outcome measure was the objective response rate defined as the proportion of patients attaining either a complete and partial response (CR and PR), respectively defined as the absence of disease ≥ 6 weeks, or as ≥ 50% reduction in tumour size for ≥ 6 weeks with no evidence of progressive disease. Other measures included; the time to treatment failure (TTF) defined as the time from start of treatment to discontinuation due to an adverse event, lack of efficacy, intolerance, cardiac toxicity, progressive disease, or death; the time to progression (TTP) defined as time from start of treatment until evidence of disease progression or death; and overall survival. After a median follow-up of 21 months, the primary outcome measure demonstrated a non-significant difference for Mycoet®▼ over epirubicin with a response rate of 46% vs. 39%, respectively (p = 0.42). Other outcomes demonstrated a significant difference in favour of Myocet®▼: TTF (5.7 vs. 4.4 months, p = 0.007), TTP (7.7 vs. 5.6 months, p = 0.022), but not for median overall survival (18.3 vs. 16.0 months, p = 0.504).

Table 1. Summary table of results from phase III studies of Myocet®▼

	Harris et al [17]		Batist et al [18]		Chan et al [20]	
	Myocet®	Doxorubicin	Myocet® + Cyclophos	Doxorubicin + Cyclophos	Myocet® + Cyclophos	Epirubicin + Cyclophos
No. patients	108	116	142	155	80	80
Objective response rate (%)	26	26	43	43	46	39
Patients with progression (%)	70	66	77	81	71	79
Median time to progression (months)	3.8	4.3	5.1	5.5	7.7	5.6
Patients with failure (%)	75	83	80	87	75	84
Median time to failure (months)	3.7	3.4	4.6	4.4	5.7	4.4
Median duration of response (months)	nr	nr	9.6	9.1	10.0	7.7
Patient survival (%)	76	68	52	57	58	62
Median duration of survival (months)	16	20	19.0	16.0	18.3	16.0
Occurrence of cardiotoxicity (%)	13	29	6	21	12	10
Cases of CHF	2	9	0	5	0	0
Median lifetime doxorubicin dose at first cardiotoxic event (mg/m^2)	785	570	> 2,220	480	nr	nr
Median time to onset of first cardiotoxic event (months)	nr	nr	> 22.0	10.0	nr	nr

CHF – congestive heart failure; Cyclophos – cyclophosphamide; nr – not reported

ADVERSE EFFECTS

Specified outcome measures in each of the phase III clinical trials related to the effects of Myocet®▼ on various cardiovascular outcomes, and these have been described in the previous section on treatment efficacy. The longest follow-up of the studies was nearly seven years and therefore the studies will have reduced capacity to identify later onset cardiotoxicity.

In the single-agent comparative study Myocet®▼ did not produce any unexpected adverse effects although there was one case of palmar-plantar erythrodysesthesia (PPE, or hand-foot syndrome) in a Myocet®▼-treated patient. [17] The most common adverse events in Myocet®▼ and doxorubicin patients respectively were: grade 2 alopecia (84% vs. 88%, p = 0.44), neutropenia (50% vs. 58%, p = 0.28), anaemia (22% vs. 26%, p = 0.53), grade 3 or 4 nausea or vomiting (13% vs. 24%, p = 0.06), grade 3 asthenia or fatigue (14% vs. 19%, p = 0.47), and thrombocytopenia (13% vs. 10%, p = 0.53). [17] Prophylactic GCSF was administered in 58% and 70% of Myocet®▼ and doxorubicin cycles, respectively. [17]

In the comparative study by Batist the most common adverse events in Myocet®▼ and doxorubicin patients respectively were: grade 2 alopecia (91% vs. 95%, p = 0.26), grade 4 neutropenia (61% vs. 75%, p = 0.02), anaemia (23% vs. 27%, p = 0.42), grade 3 or 4 thrombocytopenia (22% vs. 20%, p = 0.78), grade 3 or 4 nausea or vomiting (13% vs. 16%, p = 0.62), neutropenia-associated fever requiring IV antibiotics and/or hospitalisation (9% vs. 13%, p = 0.36), and grade 3 or 4 infection (11% vs. 8%, p = 0.33). [18]

In the comparative study of Myocet®▼ or epirubicin, plus cyclophosphamide, the most common adverse effects were, respectively; alopecia (87% vs. 85%, p = 0.82), grade 4 neutropenia (87% vs. 67%, p = 0.004), grade 4 neutropenia ≥ 7 days (26% vs. 31%, p = 0.60), anaemia (25% vs. 14%, p = 0.11), grade 3 or 4 nausea or vomiting (21% vs. 19%, p = 0.84), and injection site toxicity (1.0% vs. 10.1%, p = 0.03). [20]

Across the clinical studies the adverse events experienced were anticipated and seldom resulted in disruption of the planned treatment cycles, with the median time between cycles being the target 21 days, and total dose intensity as a proportion of the target dose being > 90%. [17,18,20]

DOSAGE, ADMINISTRATION AND COST

The recommended dose of doxorubicin for the treatment of metastatic breast cancer is 60 to 75 mg/m^2 BSA. [21]

There are various strategies for reducing the cardiotoxic effects of standard doxorubicin infusions. One method is to use a liposome encapsulated formulation, of which Myocet®▼ is one example. [16] One other liposome doxorubicin formulation is also available in the UK and this has the proprietary name Caelyx®▼ (Schering-Plough). [15] No dose adjustments are recommended for liposome formulations of doxorubicin.

Alternatively, standard doxorubicin can be combined with the iron-chelator dexrazoxane (Cardioxane®▼, Novartis). [13] The recommended dose of dexrazoxane is 20 times the doxorubicin dose or 10 times the epirubicin dose.

The final option is to use epirubicin instead of doxorubicin, with or without dexrazoxane. Epirubicin is structurally similar to doxorubicin but is typically administered at a dose 1.0 to 1.5 times that of doxorubicin, with treatment commencing at 60 to 90 mg/m^2 BSA. [22] Cardiotoxicity can be further reduced by including dexrazoxane in the epirubicin regimen. [13,23]

Both standard doxorubicin and epirubicin are available from generic manufacturers and consequently these drugs cost substantially less than the liposome formulations of doxorubicin (see Table 2).

Each of the anthracycline drugs and formulations is available in a range of strengths. Pharmaceutical aseptic compounding units will often produce a number of cytotoxic regimens in a single session thus ensuring maximum drug extraction and minimum waste from each vial. Ultimately this will reduce the total cost, but it has not been possible to include this factor into cost analyses. As well as the drug costs, additional hardware costs will be incurred from the use of needles, syringes, filters and other equipment used in the production of the cytotoxic infusion, and also intravenous infusion bags and filters, catheters, and other paraphernalia when the drug is administered. Additional drug costs will be incurred depending on the individual toxicities experienced, for example anti-emetic drugs, GCSF, antibiotics, and possibly blood transfusions. As these latter factors (hardware and drug costs) are highly variable depending on the practice of individual units and patient response it has not been possible to include these in cost analyses.

The dose, and therefore the cost, of additional drugs in any regimen (e.g. cyclophosphamide) would not be expected to vary depending on the anthracycline formulation used and these costs are not included.

The cost analyses are based on the direct drug costs of the anthracycline drugs only, or the directly associated counteragent (i.e. dexrazoxane).

Table 2. Cost of single-dose treatment with anthracyclines and dexrazoxane

	Patient BSA		
Drug (dose per m^2 BSA)	1.50 m^2	1.75 m^2	2.00 m^2
Dexrazoxane (20 times doxorubicin dose [13])	£626	£783	£783
Doxorubicin (60 mg)	£19	£21	£24
Caelyx®▼ (60 mg)	£1424	£1726	£2847
Myocet®▼ (60 mg)	£929	£1394	£1394
Epirubicin (90 mg)	£134	£152	£174

Prices obtained from NHS dictionary of medicines and devices and NHS Purchasing and Supplies Agency, March 2008.

Costs do not include VAT or take into consideration any locally negotiated discount on Caelyx®▼, Myocet®▼, or dexrazoxane.

PLACE IN TREATMENT

Myocet®▼ is a significant advance on standard doxorubicin and about 25 to 30% less costly than the only alternative liposome-encapsulated doxorubicin formulation. However it is substantially more expensive than standard doxorubicin. The available evidence for the efficacy of Myocet®▼ does not permit a robust assessment of its place in therapy, but merely confirms its advantages over standard doxorubicin. The comparative study in which epirubicin was the control treatment was flawed with respect to the doses selected. In that study the dose of doxorubicin as Myocet®▼ was greater than that typically used in UK practice (90 vs. ≤ 75 mg/m^2 BSA), a factor that may increase the efficacy but also the toxicity of the drug. This is evident in the results which demonstrated a greater efficacy for Myocet®▼ in terms of TTF and TTP but significantly greater toxicity and a greater likelihood of dose reductions. Indeed this is something that the authors themselves allude to, and ultimately it does not enable a fair assessment of the relative benefits of Myocet®▼ and epirubicin. No evidence was identified relating to the efficacy of Myocet®▼ compared to either doxorubicin or epirubicin combined with dexrazoxane.

Dexrazoxane is a costly treatment itself, which must be infused over 15 minutes and prior to chemotherapy. Even with the added cost of dexrazoxane, both doxorubicin and epirubicin are still only about one third the cost of Myocet®▼. Given the large discrepancies in cost it would be useful to have information relating to the relative efficacy and safety of each of these treatments.

Myocet®▼ may be a useful option for achieving cumulative doxorubicin doses greater than the currently recommended maximum of about 450 mg/m^2 BSA. [10] Myocet®▼ should therefore be reserved for patients who are in sufficiently robust enough health to withstand prolonged treatment with an anthracycline but would otherwise be limited by the recommended maximum cumulative dose, or for patients that demonstrate a response to an anthracycline but are not able to receive any further treatment due to the limits on cumulative exposure. It may also be useful for patients who have received prior standard doxorubicin but then require subsequent anthracycline therapy more than six months after their initial course. Ideally these situations should be investigated within the context of a clinical study.

At present there is insufficient evidence for a robust assessment of Myocet®▼ and due to the comparatively high cost of treatment its widespread use is not recommended. However it may be of benefit in a limited number of specific patients.

ARRANGEMENTS FOR PRESCRIBING

Liposomal doxorubicin can be substituted for standard doxorubicin and therefore no additional arrangements for prescribing are required. Facilities should be available to manage the possible emergence of hand-foot syndrome (PPE).

REFERENCES

1 Office for National Statistics. Registrations of cancer diagnosed in 2004, England www.statistics.gov.uk/downloads/theme_health/MB1_35/MB1_No%2035_2004.pdf (Accessed 07/02/08)

2 Cancer Research UK. Breast cancer mortality statistics 2006. http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/breast/cs_br_t2.1.xls (Accessed 08/07/08)

3 Blanks RG, Moss SM, McGahan CE et al. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. British Medical Journal 2000;321:665-9

4 Office for National Statistics. Cancer Survival, England, 1999-2004. www.statistics.gov.uk/downloads/theme_health/Survival_21_sites_1999_2003_by_age_group_v6.xls (Accessed 07/02/08)

5 Jones L, Hawkins N, Westwood M et al. Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda) for locally advanced and/or metastatic breast cancer. Health Technology Assessment 2004;8:iii, xiii-xvi, 1-143

6 Smith I, Chua S. Medical treatment of early breast cancer. I: adjuvant treatment. British Medical Journal 2006;332:34-7

7 Smith I, Chua S. Medical treatment of early breast cancer. III: chemotherapy. British Medical Journal 2006;332:161-2

8 Danesi R, Fogli S, Gennari A et al. Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. Clinical Pharmacokinetics 2002;41:431-444

9 Birtle AJ. Anthracyclines and cardiotoxicity. Clinical Oncology 2000;12:146-52

10 Horan PG, McMullin MF, McKeown PP. Anthracycline cardiotoxicity. European Heart Journal 2006;27:1137-8

11 Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Expert Opinion on Drug Safety 2006;5:791-809

12 Batist G. Cardiac safety of liposomal anthracyclines. Cardiovascular Toxicology 2007;7:72-4

13 Novartis. Summary of product characteristics. Cardioxane®▼ powder for solution for infusion (dexrazoxane). 12th September 2007 http://emc.medicines.org.uk

14 Swenson CE, Bolcsak LE, Batist G et al. Pharmacokinetics of doxorubicin administered i.v. as Myocet (TLC D-99; liposome-encapsulated doxorubicin citrate) compared with conventional doxorubicin when given in combination with cyclophosphamide in patients with metastatic breast cancer. Anti-Cancer Drugs 2003;14:239-46

15 Schering-Plough. Summary of product characteristics. Caelyx®▼ concentrate for solution for infusion (liposomal doxorubicin). 9th January 2008 http://emc.medicines.org.uk

16 Cephalon. Summary of product characteristics. Myocet®▼ powder and pre-admixtures for concentrate for liposomal dispersion for infusion (liposomal doxorubicin). 19th June 2007 http://emc.medicines.org.uk

17 Harris L, Batist G, Belt R et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. Cancer 2002;94:25-36

18 Batist G, Ramakrishnan G, Rao CS et al. Reduced cardiotoxicity and preserved antitumour efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. Journal of Clinical Oncology 2001;19:1444-54

19 Batist G, Harris L, Azarnia N et al. Improved anti-tumor response rates with decreased cardiotoxicity of non-pegylated liposomal doxorubicin compared with conventional doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin: results of a retrospective analysis. Anti-Cancer Drugs 2006;17:587-95

20 Chan S, Davidson N, Juozaityte E et al. Phase III trial of liposomal doxorubicin and cyclophosphamide compared with epirubicin and cyclophosphamide as first-line therapy for metastatic breast cancer. Annals of Oncology 2004;15:1527-34

21 Pharmacia Limited. Summary of product characteristics. Doxorubicin Rapid Dissolution. 6th March 2008. http://emc.medicines.org.uk

22 Hospira UK Limited. Summary of product characteristics. Epirubicin hydrochloride 2 mg/ml injection. 9th August 2006. http://emc.medicines.org.uk

23 Venturini M, Michelotti A, Del Mastro L et al. Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. Journal of Clinical Oncology 1996;14:3112-20

SUMMARY TABLE OF PHASE III STUDIES OF MYOCET®▼

Key: BSA – body surface area, CHF – congestive heart failure, CR – complete response, ECOG – Eastern Cooperative Oncology Group, LVEF – left ventricular ejection fraction, MC – multicentre, MI – myocardial infarction, PR – partial response, RCT – randomised controlled trial

Reference	Design	Intervention (patient numbers)	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
17. Harris et al	RCT, MC	Myocet® 75 mg/m^2 BSA (n = 108) or Doxorubicin 75 mg/m^2 BSA (n = 116) Cycles once every three weeks	Age ≥ 18 years Metastatic breast cancer ECOG status ≤ 2 Life expectancy ≥ 3 months Adequate haematological parameters Adequate liver and renal function LVEF ≥ 50% predicted	Non-breast malignancy other than cervical or non-melanoma skin cancer Bone disease only Adjuvant doxorubicin if lifetime dose > 300 mg/m^2 BSA Any cytotoxic chemotherapy ≤ 6 months History of CHF, serious arrhythmia, or MI ≤ 6 months Pregnancy & lactation	Objective response rate, defined as the sum of CR and PR CR defined as the complete disappearance of all evidence of disease ≥ 6 weeks PR defined as ≥ 50% decrease in sum of dimensions of lesions ≥ 6 weeks with no evidence of progression	Objective response rate of 26% in both treatment groups Myocet® vs. doxorubicin respectively: CR 0% vs. 2% PR 26% vs. 24%	Myocet® vs. doxorubicin (p > 0.05 unless stated). Anaemia: 22 vs. 26% Thrombocytopenia: 13 vs. 10% Neutropenia: 50 vs. 58% Infection (grade ≥ 3): 5 vs. 12% Neutropenic fever: 11 vs. 9% Nausea/vomiting (grade ≥ 3): 13 vs. 24% Alopecia (grade 2): 84 vs. 88% Asthenia/fatigue (grade ≥ 3): 14 vs. 19% Stomatitis/mucositis (grade ≥ 3): 9 vs. 14% Cardiotoxicity*: 13 vs. 29% (p = 0.0001)
18. Batist et al	RCT, MC	Cyclophosphamide 600 mg/m^2 BSA plus Myocet® 60 mg/m^2 BSA (n = 142) or Doxorubicin 60 mg/m^2 BSA (n = 155) Cycles once every three weeks	Age ≥ 18 years Metastatic breast cancer ECOG status ≤ 2 Life expectancy ≥ 3 months Adequate haematological parameters Adequate liver and renal function LVEF ≥ 50% predicted	Non-breast malignancy other than cervical or non-melanoma skin cancer Adjuvant doxorubicin if lifetime dose > 300 mg/m^2 BSA and < 6 months elapsed since last dose Any cytotoxic chemotherapy ≤ 6 months History of CHF, serious arrhythmia, or MI ≤ 6 months Pregnancy & lactation	Objective response rate, defined as the sum of CR and PR CR defined as the complete disappearance of all evidence of disease ≥ 6 weeks PR defined as ≥ 50% decrease in sum of dimensions of lesions ≥ 6 weeks with no evidence of progression	Objective response rate of 43% in both treatment groups Myocet® vs. doxorubicin respectively: CR 5% vs. 6% PR 38% vs. 37%	Myocet® vs. doxorubicin (p > 0.05 unless stated) Anaemia: 23 vs. 27% Thrombocytopenia: 22 vs. 20% Neutropenia: 61 vs. 75% (p = 0.02) Infection (grade ≥ 3): 11 vs. 8% Neutropenic fever: 9 vs. 13% Nausea/vomiting (grade ≥ 3): 13 vs. 16% Alopecia (grade 2): 91 vs. 95% Asthenia/fatigue (grade ≥ 3): 6 vs. 5% Stomatitis/mucositis (grade ≥ 3): 4 vs. 7% Cardiotoxicity*: 6 vs. 21% (p = 0.0001)

Reference	Design	Intervention (patient numbers)	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
20. Chan et al	RCT, MC	Cyclophosphamide 600 mg/m^2 BSA plus Myocet® 75 mg/m^2 BSA (n = 80) or Epirubicin 75 mg/m^2 BSA (n = 80) Cycles once every three weeks ≤ 8 cycles	Age ≥ 18 years Metastatic breast cancer ECOG status ≤ 2 Life expectancy ≥ 3 months Adequate haematological parameters Adequate liver and renal function LVEF ≥ 50% predicted	Non-breast malignancy other than cervical or non-melanoma skin cancer Bone or brain metastases Any adjuvant therapy ≤ 6 months History of previous anthracycline therapy, or other cytotoxic chemotherapy for metastatic disease History of significant cardiac problems Pregnancy & lactation	Objective response rate, defined as the sum of CR and PR CR defined as the complete disappearance of all evidence of disease ≥ 6 weeks PR defined as ≥ 50% decrease in sum of dimensions of lesions ≥ 6 weeks with no evidence of progression	Myocet® vs. doxorubicin respectively: Objective response rate of 46% vs. 39% (p = 0.42) CR 11% vs.11% PR 35% vs. 28%	Myocet® vs. epirubicin (p > 0.05 unless stated) Anaemia: 25 vs. 14% Thrombocytopenia: 4 vs. 3% Neutropenia: 87 vs. 67% (p = 0.004) Infection (grade ≥ 3): 7 vs. 1% Neutropenic fever: 5 vs. 1% Nausea/vomiting (grade ≥ 3): 21 vs. 19% Alopecia (grade 2): 87 vs. 85% Asthenia/fatigue (grade ≥ 3): 0 vs. 1% Stomatitis/mucositis (grade ≥ 3): 7 vs. 0% (p = 0.03) Cardiotoxicity*: 12 vs. 10%

* : Cardiotoxicity was defined as a decrease in resting LVEF of ≥ 20 points from baseline to a final value of ≥ 50%, or a decrease of ≥ 10 points from baseline to a final value < 50%, or clinical evidence of CHF.