Draft benefit definition: Locally recurrent or metastatic breast cancer

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Disclaimer:

The breast cancer benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore regulation 15h may be applied for patients who are inadequately managed by the stated benefits. The procedure codes are just an indication of applicable procedure codes, however some significant procedure codes may not have been included. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs, supportive medication nursing care. However, these interventions form part of care and are prescribed minimum benefits.

1. Introduction

1.1 The legislation governing the provision of the prescribed minimum benefits (PMBs) are contained in the regulations enacted under the Medical Schemes Act 131 of 1998. In respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries find it difficult to know their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2 The benefit definition project is coordinated by the Council for Medical Schemes (CMS) and aims to define the PMB package and to guide the interpretation of the PMB provisions by relevant stakeholders. The guidelines are based on the available evidence of clinical and cost effectiveness taking into consideration affordability constraints and financial viability of medical schemes in South Africa.

2. Scope and purpose

2.1 This is a recommendation for the diagnosis, treatment and care of individuals with advanced breast cancer in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2 The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into considerations evidence based medicine, affordability and in some instances cost-effectiveness

Table 1: Possible ICD10 codes for identifying breast cancer

ICD 10	*WHO description*
Z12.3	Special screening examination for neoplasm of breast
C50.0	Malignant neoplasm, nipple and areola
C50.1	Malignant neoplasm, central portion of breast
C50.2	Malignant neoplasm, upper-inner quadrant of breast
C50.3	Malignant neoplasm, lower-inner quadrant of breast
C50.4	Malignant neoplasm, upper-outer quadrant of breast
C50.5	Malignant neoplasm, lower-outer quadrant of breast
C50.6	Malignant neoplasm, axillary tail of breast
C50.8	Malignant neoplasm, overlapping lesion of breast
C50.9	Malignant neoplasm, breast, unspecified

3. Epidemiology

3.1 Breast cancer is the most common cancer in women both in the developed and less developed world. In 2012, 1.7 million women were diagnosed with breast cancer while the prevalence stood at 6.3 million women. According to WHO Breast cancer was also the most common cause of cancer death among women with 508 000 deaths in 2011 and 522 000 deaths in 2012. Breast cancer was also the most frequently diagnosed cancer among women in 140 of 184 countries worldwide[1].

3.2 Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries. Incidence rates of breast cancer vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In contrast to Eastern Africa, breast cancer was the most commonly diagnosed cancer and the leading cause of cancer death among women in Southern Africa (9000 cases, 4500 deaths)[2].

3.3 Breast cancer survival rates vary greatly worldwide, ranging from 80% or more in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries[3]. The low survival rates in less developed countries can be explained mainly by the lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities. Currently in South Africa 10% of patients with breast cancer present with stage 1 diseases and the remainder presents with 30% each for stages two three and four[4]. According to the South African National Cancer Registry, Breast cancer was the most prevalent cancer amongst women with a lifetime risk of 1:35[5].

4. Diagnostic procedures

4.1 Minimal staging workup for women who present with metastatic breast cancer or recurrent disease includes a history and physical examination, haematology and biochemistry tests, and imaging of chest, abdomen, and bone[6-8].

4.2 Complete history of women with recurrent disease or metastatic breast cancer includes detailed history of the primary tumour, its biology, management and status at the last follow up, duration, previous sites of involvement, previous treatment and their side effects, current symptoms and performance status.

4.3 Complete blood count, liver and renal function tests, alkaline phosphatase, LDL, calcium and urinary protein tests are indicated if applicable.

4.4 Detailed physical examination to is indicated to determine the extent of the disease [6, 8, 9].

4.5 Oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status is PMB level of care if receptor status was not assessed at initial diagnosis.

4.6 Chest x-ray is indicated for patients with clinically positive axillary nodes, large tumours, and/or clinical signs laboratory values suggesting metastases to determine the presence of pulmonary metastases [8].

4.7 Bone scan is indicated for patients with clinically positive axillary nodes, large tumours, clinical signs and/or laboratory values suggesting metastases, bone pain to determine the presence of metastases to bone [8, 10]

4.8 Computed tomography (CT scan) is indicated for patients with clinically positive axillary nodes, large tumours, and clinical signs and/or laboratory values suggesting metastases to determine metastatic regions [11]

4.9 [18F]-fluorodeoxyglucose Positron emission tomography–computed tomography (FDG-PET/CT) is indicated when conventional methods are not conclusive in determining metastases [12, 13]. According to the Radiological Society of South Africa, PET-CT scan is only indicated if:

- There is a significant chance of distal disease as determined by axillary dissection or where conventional imaging is equivocal.
- PET scan can result in up to 57% change of stage and management compared to conventional imaging.
- Has high accuracy (86% vs. 77% for CT alone) for nodal and distal metastases in patient with infiltrating ductal carcinoma.

Table 2: Diagnostic work-up for metastatic breast cancer

	Procedure	Indication
Blood tests	Full blood count	
Liver function tests	Total Bilirubin	Baseline tests to assess possible liver involvement
	Albumin	
	Alanine transminase (ALT)	
	Aspartate transminase (AST)	
	Alkaline Phosphatase (ALP)	
Renal function tests	Urea	Assessment of possible obstructive renal symptoms
	Creatinine	
	Electrolyte	
	Calcium	
	Phosphates	
Histology	ER, PR and HER2 determination	Indicated if receptor status was not assessed at initial diagnosis
Imaging	Chest X-ray	To determine the presence of pulmonary metastases.
	Bone Scan	To determine the presence of metastases to bone
	CT Scan	To determine metastatic regions

5. Management

5.1 Patients with metastatic disease are those with stage IV disease.

5.2 Advanced breast cancer is treatable but still generally incurable. Standard therapies provide palliation or prolonged symptom free survival.

5.3 Management of metastatic prostate cancer is a prescribed minimum benefit and care aims at improving quality of life and minimising the acute effects of cancer. In the explanatory notes of the Act, solid organ tumour will be regarded as treatable where:

a. They involve only the organ of origin and have not spread to adjacent organs

b. There is no evidence of distant metastatic spread

c. They have not, by means of compression, infarction, or other means brought about irreversible and irreparable damage to the organ from which they originated or another vital organ or

d. If points (a-c) do not apply, there is a well demonstrated five years survival rates

5.4 The 5 year survival rate of metastatic breast cancer as reported by the American Cancer Society is 22%.

5.5 The treatment of advanced breast cancer includes a combination of systemic chemotherapy, hormonal therapy, radiotherapy and psychosocial support to optimize the outcomes of treatment.

5.6 Endocrine therapy

5.6.1 Endocrine therapy is PMB level of care in patients with ER-positive advanced breast cancer.

5.6.2 Tamoxifen is indicated in premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with Tamoxifen.

5.6.3 Aromatase Inhibitors are indicated in postmenopausal women with ER-positive breast cancer with no prior history of endocrine therapy and treatment with Tamoxifen.

5.6.4 Luteinizing hormone-releasing hormone (LHRH) agonists are indicated in premenopausal ER+ patients with Tamoxifen contraindication.

Evidence

Benedict et al. [21] evaluated the cost-effectiveness of aromatase inhibitors (AIs)—Letrozole, Exemestane, Anastrozole, and fulvestrant in metastatic hormone receptor-positive breast cancer

relative to either Tamoxifen or Megestrol as first- and second-line therapy, respectively. The analyses suggested, that AIs were highly cost-effective in the metastatic setting irrespective of country and the line of therapy. The review was judged of relative good scientific quality as suggested by the score (70 %) obtained using the modified AMSTAR tool.

Foster et al. [20] assessed the economic impact of various metastatic breast cancer (MBC) treatments including hormonal and targeted therapies. The results of the economic evaluations included in the review suggested that endocrine therapies were very cost-effective. Specifically, newer AIs (Anastrozole and Letrozole) were found to be cost-effective in the first-line therapy when compared to Tamoxifen, in patients with hormone receptor-positive breast cancer.

5.7 Chemotherapy

5.7.1 Systemic sequential chemotherapy is indicated in patients with advanced breast cancer.

5.7.2 Combination chemotherapy is indicated in patients with advanced disease with life threatening visceral disease, rapid progression and when rapid symptom control is necessary[14] [6].

Table 3: Chemotherapy for management of metastatic disease.

Chemotherapy[14]	**Indication**
Doxorubicin (DOXO 75)	First line adjuvant therapy
Docetaxel (DOCE 75)	
Paclitaxel/Doxorubicin,/Cyclophosphamide (PAC 225)	
Paclitaxel/Doxorubicin,/Cyclophosphamide (PAC 80)	
Capecitabine	Anthracycline and Taxane contraindicated
Uracil-Tegafur (UFT)	

CAF28	Combination therapy in life threatening visceral disease, rapid progression and whenever rapid symptom control is necessary
Cyclophosphamide, Methotrexate, 5-Fluorouracil (CMF)	
FAC	
CIS-75 GEM	
Vinorelbine (VINO)	Second line therapy
cis-diamminedichloroplatinum(II)	
Mitoxantrone, Methotrexate, Mitomycin C (MMM)	
Vinorelbine/Capecitabine (VINO/CAP)	
VINBLAS/MITO C	

Clinical Evidence

Several studies have contributed to clarifying the relative role of a single sequential therapy versus a combination therapy for metastatic breast cancer. The E1193 Intergroup Trial randomized 739 chemotherapy naive breast cancer patients to receive doxorubicin 60 mg/mq or paclitaxel 175 mg/mq as single agents or the combination of doxorubicin (50 mg/mq) and paclitaxel (150 mg/mq). Patients who received single agent chemotherapy were crossed over to the other agent as the disease progressed. Despite the statistically significant improvements in response rate and time to treatment failure for combination as opposed to single-agent therapy, there was no significant difference in overall survival and the quality of life between the groups.

In another study by O'Shaughnessy et al. 511 antracycline-pretreated MBC patients were randomized to receive docetaxel and capecitabine or docetaxel as a single agent [7]. A higher response rate, improved time to progression and the overall survival for the combination treated group was reported. Only 17% patients initially treated with docetaxel subsequently received capecitabine at progression.

This unfortunately was a concern as it does not allow an accurate comparison between the concomitant and sequential administration of both drugs.

Heidemann et al. studied 260 patients randomized to mitoxantrone 12 mg/mq vs FEC (5FU 500 mg/mq, Epirubicin 50 mg/mq, Cyclophosphamide 500 mg/mq) every 3 weeks, in first line chemotherapy [9]. The treatment schedule was continued until complete remission plus two cycles, or until disease progression. Second line chemotherapy was planned and consisted of mitomycin in combination with vindesine and prednisolone. Third line chemotherapy was left to the discretion of the oncologist, assuming that subsequent lines of chemotherapy would not contribute significantly to the overall survival. In order to measure palliation and quality of life and the opinion of patients and oncologists, a Brunner's score was adopted. No statistical differences were detected in terms of response rate, time to response, time to best response, time to progression and overall survival.

Furthermore the Preliminary results for 105 recruited patients in a trial, by Soto et al showed no significant differences between the three arms in terms of overall survival. In this study 217 antracycline- pretreated MBC patients were randomized to receive capecitabine plus docetaxel or paclitaxel in combination, or capecitabine followed by a taxane at disease progression [8]. A meta-analysis by Fossati et al. 15 studies comparing combination chemotherapy with single agent treatment were evaluated. The authors found that the response rate and overall survival was higher in the combination chemotherapy pooled data [3].

5.8 Managing complications

5.8.1 Bisphosphonates are indicated in patients with bone metastases to prevent skeletal-related events and to reduce pain [15-17].

5.8.2 Radiological assessment is indicated in patients with persistent and localized bone pain to determine impending or actual pathological fractures [16, 18].

5.8.3 MRI is indicated to assess neurological symptoms and signs which suggest the possibility of spinal cord compression [8]. MRI is not routinely recommended in asymptomatic patients with previous diagnosis of malignancy.

5.8.4 External beam radiotherapy is indicated in patients with bone metastases and pain.

5.8.5 Surgery or radiosurgery is indicated in patients with single or small number of potentially resectable brain metastases[19].

5.8.6 Lymphoedema complex decongestive therapy (CDT) is indicated for the management of lymphoedema[20].

Table 4: Management of side effects of treatment for breast cancer

Local symptoms	***Treatment modality***
Local pain	External beam radiotherapy analgesia (Opiods plus adjuvant antidepressant; anti-seizure and NSAIDS)
Spinal cord compression	This is an emergency condition and patients must have an MRI , steroidal treatment and surgery and/or radiotherapy
Diffuse pain	Hormonal therapy/chemotherapy
Inflammatory syndrome	Steroids and NSAIDS
Bone metastasis	Bisphosphonates to reduce pain
Brain metastasis	Surgery, whole breast radiation therapy (WBRT)
Lymphoedema	CDT

5.9 Follow-up and palliative care

5.9.1 Follow-up for patients with MBC is indicated to provide best possible palliation of symptoms and to maintain quality of life.

5.9.2 Follow-up every 2-4 months is indicated for patients on endocrine therapy[6]

5.9.3 Follow-up every two cycles is indicated for patients on chemotherapy.

5.9.4 Response evaluation is indicated if progression is suspected due to aggravation or appearance of new symptoms and/or significant increase in tumour marker levels [6].

5.9.5 Serum tumour makers may be useful in monitoring response particularly in absence of easily measurable disease. Full blood count, liver and renal function tests and calcium tests are PMB level of care for monitoring response.

5.9.6 Palliative care is PMB level of care for uncontrolled local disease to control pain and relieve other symptoms [16].

5.9.7 Pain treatment is indicated for patients in need of pain relief [16, 19].

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