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CONSENSUS

Mexican breast cancer consensus. Multidisciplinary care in breast cancer

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Abstract

Breast cancer impacts various spheres of the patient's life and their family and social environment. It is a complex disease that requires a multidisciplinary approach both for diagnosis and treatment, as well as for managing mediate and late toxicity from systemic treatment and radiotherapy, as well as psychological aspects. Palliative care and pain management are being incorporated earlier and earlier into treatment for the benefit of patients. Geneticists have now been incorporated into this multidisciplinary approach due to advances in genotyping and targeted therapies. The dissemination of this consensus contributes to the updating and homogeneity of breast cancer management criteria and the objective of this article is to present the update on the multidisciplinary management of breast cancer.

Keywords: *Breast cancer. Multidisciplinary treatment. Consensus.*

Consenso mexicano de cáncer mamario. Cuidados multidisciplinarios en cáncer de mama

Resumen

El cáncer mamario impacta en diversas esferas de la vida del paciente y su entorno familiar y social. Se trata de una enfermedad compleja que requiere un abordaje multidisciplinario tanto para el diagnóstico como para el tratamiento, así como

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en lo relativo al manejo de la toxicidad mediata y tardía del tratamiento sistémico y la radioterapia y también los aspectos psicológicos. Los cuidados paliativos y el manejo del dolor se incorporan cada vez más tempranamente al tratamiento en beneficio de los pacientes. Actualmente se ha incorporado a los genetistas a este abordaje multidisciplinario debido a los avances en genotipificación y terapias dirigidas. La difusión de este consenso contribuye a la actualización y homogeneidad de criterios de manejo del cáncer mamario y el objetivo de este artículo es el presentar la actualización en el manejo multidisciplinario del cáncer de mama.

Palabras clave: *Cáncer de mama. Cuidados multidisciplinarios. Consenso.*

Systemic and locoregional management mid-term/late toxicity

Mid- and long-term systemic toxicities

Timely diagnosis and new therapeutic advances implementation have improved the prognosis of patients with early breast cancer and significantly increased the number of survivors. This is why toxicities caused by medical treatment are of particular importance, and being familiar with their recommended management is essential, given the huge impact they have on survivors' quality of life[1].

Cardiotoxicity

Anthracyclines

Cardiotoxicity related to the use of anthracyclines occurs as systolic dysfunction resulting from damage to the myocyte and its replacement by fibrotic tissue due to oxidative stress and topoisomerase II inhibition, observed on echocardiogram as a decrease in left ventricular ejection fraction (LVEF). This toxicity is dose-dependent and considerably increases when doxorubicin cumulative doses are higher than 400 mg/m^2, and 900 mg/m^2 in the case of epirubicin. Its incidence is variable and depends on different associated factors and the method cardiac function is evaluated with; it has been reported in adults within a range from 7% due to LVEF to 45% when associated with cardiac strain[2].

Associated risk factors:

- Age older than 65 years.
- History of hypertension, diabetes or cardiac comorbidities.
- Obesity.
- High cumulative doses (1% risk with doses of 240 mg/m^2, 5% with 400 mg/m^2 and drastic risk increase with ≥ 550 mg/m^2 of adriamycin).
- History of radiation to the mediastinum.
- Combination with other cardiotoxic agents.

Among the clinical characteristics that can be associated with cardiotoxicity due to anthracyclines, the following can be mentioned:

- Congestive heart failure.
- Palpitations.
- Arrhythmias.
- Elevation of biomarkers such as troponin, type B natriuretic peptide.

Anthracycline-associated heart failure is considered a diagnosis of exclusion and should be suspected in the context of a patient who received anthracyclines as cancer treatment and who has associated risk factors. Anthracycline-associated ventricular dysfunction is regarded as significant when there is a > 10% decrease from a baseline LVEF ≤ 40%, or ≤ 15% from a baseline LVEF < 50%[3].

Recommendations:

- Perform echocardiogram to obtain LVEF and strain in all patients who are to receive treatment with anthracyclines. If echocardiogram is not available or cannot be performed, nuclear imaging techniques (MUGA) or cardiac magnetic resonance are suggested for LVEF evaluation.
- Do not exceed anthracycline recommended doses.
- Avoid concomitant use of cardiotoxic agents.
- Consider the use of chemotherapy regimens without anthracyclines in patients with very high risk of cardiotoxicity.
- Consider serial monitoring with LVEF or strain depending on patient risk factors.
- Do not systematically use cardioprotective agents (angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor antagonists, statins, acetylsalicylic acid), unless they have additional indications.
- Clinical monitoring of symptoms and, where appropriate, timely referral to the cardiology department.

Trastuzumab and other anti-HER2 agents

Cardiotoxicity caused by anti-HER2 agents is an constant concern when these treatments are administered.

However, it is generally considered reversible. Its pathophysiology is not fully understood, but it is not dose-dependent and is related to the damage caused by anti-HER2 blockade at the level of cardiac myocytes. The incidence of heart failure due to anti-HER2 therapy is 1.5 to 5%; LVEF asymptomatic decrease can range from 4 to 20%. Risk factors are similar to those mentioned for cardiotoxicity due to anthracyclines[4,5].

Management with beta blockers and ACEI can improve LVEF; however, these drugs are not systematically recommended[6].

Recommendations:

- Echocardiogram, MUGA or, in special cases, cardiac magnetic resonance prior to starting anti-HER2 treatment and every three months until its completion (months 0, 3, 6, 9 and 12). In patients with metastatic disease, personalized surveillance is recommended, given that many receive anti-HER2 therapy for very long periods.
- If there is LVEF decrease (< 40% or a drop of ≥ 10% from baseline), treatment should be discontinued, and heart failure be addressed.
- If LVEF improves, resuming treatment is possible under close supervision by the cardiology department.

Treatment-associated myeloid neoplasms

Acute myelocytic leukemia and myelodysplastic syndrome have been associated with the use of agents that cause DNA damage, such as cytotoxic chemotherapy, and occur five to seven years after treatment. The risk associated with the use of taxanes is not fully defined, given the relatively recent introduction of these drugs[7].

After antineoplastic therapy, 5-year cumulative rate of myeloid neoplasms years is 0.24%, and it increases to up to 0.48% 10 years after treatment conclusion. In comparison with patients treated with surgery alone, those who receive chemotherapy have a 6.8-fold higher risk, and it increases 7.6 times if they are treated with chemotherapy and radiotherapy (RT)[8].

Clinical presentation is variable, but most patients exhibit manifestations that resemble acute leukemia or myelodysplastic syndrome, with signs and symptoms associated with pancytopenia. Treatment-associated myeloid neoplasia should be suspected in patients with previous exposure to cytotoxic agents and who present with clinical and laboratory manifestations (pancytopenia, leukocytosis, blasts or immature cells in peripheral blood or bone marrow) consistent with leukemic syndromes[9].

Finally, with the recent approval by the Food and Drug Administration (FDA) of poly(ADP)-ribose polymerase (PARP) inhibitors for adjuvant treatment of patients with germline *BRCA1/2* pathogenic variants, there is the possibility of myelodysplastic syndrome to develop in this group. Although reports of this adverse event are < 1%, further long-term follow-up is required[10].

Chemotherapy-induced neuropathy

Neuropathy is a common complication in patients receiving chemotherapy treatment, mainly with taxanes, and is an important cause of quality of life deterioration. Neuropathy is considered to be dose-dependent; its incidence is 13 to 27% and varies depending on the type and frequency of chemotherapy used. Factors associated with this toxicity include: advanced age, ethnicity, obesity, diabetes mellitus and history of alcohol abuse[11]. Its clinical manifestations are mainly sensory (dysesthesia, paresthesia, etc.) and, in severe cases, it can be disabling and/or permanent. To date, there is no efficacious preventive method, and therapeutic options have limited benefit[12,13].

Prevention:

- Maintain an appropriate exercise routine for each patient before, during and after treatment.
- In patients who have received taxanes, check vitamin D levels and supplement in case of deficiency.

Treatment:

- Adjustment and reduction of cytotoxic agent doses.
- Physical therapy and rehabilitation intervention. Although there is no solid evidence, regular exercise is considered to be a beneficial habit for all patients.
- In small studies, duloxetine at a dose of 30 mg per day for 1 week with an increase to 60 mg per day for 4 weeks has been shown to significantly reduce pain and improve quality of life in patients who received taxanes and platinums[14].
- Gabapentinoids have shown limited benefit in clinical trials; their effect appears at high doses and after weeks to months of treatment. Their administration is limited by the drowsiness and fatigue they cause[15].
- Opioids in severe cases.
- Antidepressants: nortriptyline, venlafaxine and fluoxetine lack evidence in patients with neuropathy associated with the use of taxanes[16].
- Acupuncture has had limited data, but the possibility of benefit for some selected patients is not ruled out[17].
- Relaxation and occupational therapy.
- Electrical neurostimulation and massages.

Fatigue

This is the name given to a persistent sensation of tiredness that is not proportional to physical activities. It occurs in up to 80% of patients treated with chemotherapy and hormone therapy and can persist for 6 to 12 months after treatment conclusion in up to 30% of patients. Therapeutic strategies are limited, with improvements occurring slowly[18]. In patients with metastatic disease, given the duration of treatment, fatigue is not only a common problem, but also constant in many patients.

Recommendations:

- Assess for the presence of fatigue at regular intervals.
- If fatigue is moderate-severe, rule out other causes (disease recurrence, wakefulness-sleep disturbances, depression, anxiety, pain, nutritional abnormalities, hypothyroidism, vitamin D deficiency, anemia, etc.) and treat accordingly.

Interventions:

- Increase in physical activity appropriate for each patient and on a regular basis (150 minutes of moderate aerobic exercise per week and two to three strength training sessions)[19].
- For patients who are not in conditions to exercise, walking or other physical therapy is recommended.
- Cognitive and psychosocial therapies. Relaxation techniques, support groups, etc.[20].
- Mind-body interventions: yoga, acupuncture, massage.
- Pharmacological treatment: it should only be considered when all previously mentioned alternatives have had no impact. Modafinil or methylphenidate can help in cases of severe fatigue. Evidence suggests that symptom improvement is common when modafinil is used during treatment, with limited efficacy in patients who have concluded therapy[21,22].

Cognitive dysfunction

The causes of this complex toxicity, which occurs in the medium and long term, are so far unclear; however, it can occur with chemotherapy and endocrine therapy treatment. There are reports indicating that 17 to 75% of women suffer cognitive changes owing to the treatment and to the impact caused by the diagnosis. Cognitive dysfunction can occur as memory impairment, brain fog, difficulty concentrating, etc. Currently, there are no proven interventions for the prevention and management of cognitive disorders and international guidelines do not propose specific indications. In patients with persistent cognitive impairment, neurocognitive evaluation is essential[23,24].

Recommendations:

- Optimize modifiable factors that might increase cognitive impairment (sleep, exercise, appropriate nutrition, stress reduction).
- Physical exercise, occupational and relaxation therapy.
- Cognitive rehabilitation based on brain training through computer programs assisted by a neuropsychologist[25].

Medical treatment-induced menopausal symptoms

The prevalence of climacteric symptoms induced by chemotherapy and hormone therapy (hot flashes, night sweats, vaginal dryness and atrophy, incontinence, dyspareunia, insomnia, irritability, arthralgia, fatigue) varies according to age, the type of endocrine treatment, patient menopausal status and the number of administered chemotherapy cycles. These symptoms can have an incidence as high as 77% for vasomotor symptoms[26].

Sexual life in general may be less enjoyable due to body image changes and use of systemic therapies that modify the hypothalamic-pituitary-adrenal (HPA) axis and are associated with decreased libido[27].

Hormone replacement therapy (HRT) for the treatment of menopausal symptoms has controversial evidence, since variables in these studies are hard to control (oral or vaginal HRT, estrogens or combined estrogens, administration time, etc.) and sometimes they are not reported (clinical stage, lymph node status, receptor status, etc.)[28].

Although this evidence is not conclusive, the use of HRT is deemed to affect patient prognosis, increasing the possibility of breast cancer recurrence, both in general and locoregionally[29]. Based on the above, the present consensus considers that the use of HRT is contraindicated in women who are breast cancer survivors.

General recommendations:

- Smoking cessation and alcohol intake limitation.
- Physical exercise.
- Paused breathing, muscle relaxation, meditation, yoga.
- Cognitive-behavioral therapy.
- Hypnosis.
- Acupuncture.
- The use of venlafaxine, desvenlafaxine, paroxetine, citalopram and escitalopram has an effect on the control of hot flashes; however, there are no studies comparing them against each other. The use of venlafaxine and citalopram is preferred due to their lower interaction with CYP2D6, which is particularly relevant in patients treated with tamoxifen[30].

- Gabapentin and pregabalin have been shown to reduce vasomotor symptoms by up to 46 and 71%, respectively. However, their adverse effects limit the dosage and widespread use.
- Water-based vaginal lubricants, without hormone therapy, to reduce discomfort during the day and sexual activity. In case of dyspareunia, lubricants and gels with lidocaine can be used to reduce discomfort[31].
- Other non-pharmacological measures include the use of vaginal dilators, vaginal exercises and vaginal laser, with the latter method showing promising, but uncertain. long-term results[32].
- The use of vaginal estrogens can be useful at short intervals for the treatment of refractory vaginal dryness[33].

Chemotherapy-induced ovarian failure

All patients of childbearing age should receive counseling on the probable loss of ovarian function and, if possible, be referred to an oncofertility specialist. Successful cryopreservation methods and ovarian stimulation and protection protocols are currently available. There is evidence that goserelin, simultaneously administered with chemotherapy, helps preserve ovarian function[34]. In the case of survivors with breast cancer, limited evidence suggests that pregnancy after treatment does not increase recurrence rates, and neither does it compromise the baby's health. Patients who wish to become pregnant are advised to do it two to three years after chemotherapy conclusion. All of them should receive close counseling from their oncologist and their gynecologist[35].

Musculoskeletal events

The use of aromatase inhibitors is related to myalgia, arthralgia, joint stiffness and carpal tunnel syndrome, among other musculoskeletal events[36]. These undesirable events can be severe in up to one third of patients and require treatment discontinuation in 10 to 20% of cases[37].

Recommendations:

- Regular and appropriate exercise for each patient, as well as a physical rehabilitation program.
- Non-steroidal anti-inflammatory drugs for pain control.
- Acupuncture.
- Duloxetine showed pain improvement at 12 weeks of treatment[38].
- Change from endocrine therapy to tamoxifen.
- In selected cases, temporary discontinuation for 2 to 8 weeks or switching to a different aromatase inhibitor may improve symptoms[39].

Weight increase

Maintaining an adequate weight plays an important role in breast cancer patients' follow-up and prognosis. Obesity and weight gain have been associated with an adverse prognosis, and even with a reduction of adjuvant hormone therapy efficacy, since body mass index increase can prevent ovarian suppression due to an increase in fatty tissue estrogen synthesis. The most efficient intervention is multidisciplinary management with regular physical activity, change of habits, diet modification and cognitive-behavioral therapy[40].

Treatment-associated diarrhea

Treatment-associated diarrhea is normally related to chemotherapy; however, the use of new therapies for breast cancer adjuvant treatment (neratinib, abemaciclib, pertuzumab, capecitabine) has been strongly associated with this adverse event. Although grade 3 or 4 toxicity is rare, severe diarrhea causes a decrease in quality of life and, in severe cases, it can be life-threatening[41]. Although the pathogenic mechanisms of diarrhea are different between these medications, measures to improve/decrease diarrhea are shared, and prevention of diarrhea should be considered when prescribing agents such as neratinib[42]. Educating patients about management with antidiarrheal agents is essential for adequate control.

- Uncomplicated diarrhea (without fever, without severe abdominal pain or bleeding): outpatient treatment with oral hydration, loperamide and other antidiarrheals. In case of persistence or quality of life compromise, dose reduction should be considered.
- Complicated diarrhea: hospital admission, use of intravenous solutions, electrolyte evaluation, consider *Clostridium difficile* infection. Dose reduction or treatment discontinuation should be considered.

Immune-related adverse events

The use of immune checkpoint inhibitors is associated with immune-related adverse events (irAEs). Their incidence and specific type of toxicity is variable. However, clinical trials describe some degree of toxicity ranging from 15 to 90% in all neoplasms, and specifically in breast cancer, it can be as high as 40%, with rates of grade 3 irAE closer to 12%[43].

irAEs include skin-related, gastrointestinal, endocrine toxicities, and other less common inflammatory events. Their appearance during treatment with immunotherapy is unclear and depends on the adverse event that develops, since it

can go from the second week of administration to weeks or months after treatment conclusion. Clinical suspicion is essential for diagnosis, and, in certain cases, the immune checkpoint inhibitor must be discontinued, and immunoregulators (glucocorticoids, mycophenolate mofetil, tumor necrosis factor-alpha antagonists, etc.) must be used for the treatment of irAEs. It is important to monitor symptoms and thyroid and adrenal function tests during treatment every 4 to 6 weeks[44]. The incorporation of a multidisciplinary team (rheumatologists, pulmonologists, endocrinologists, gastroenterologists, etc.) is essential for irAEs appropriate care. Reintroduction of an immune checkpoint inhibitor in case of an AE that required immunotherapy discontinuation, must be individualized based on the response to immunoregulators, severity of the event and available treatment options[45].

Bone antiresorptive agents

Bisphosphonates and denosumab are useful therapies for the management of patients at high risk of developing osteoporosis and fractures, as well as for the management of patients at high risk of recurrence. Although therapy with antiresorptive agents is well tolerated, their use can be associated with undesirable and infrequent adverse effects.

- Hypocalcemia: its incidence varies from 6.8 to 11.4% and is more frequent with denosumab. To minimize the risk, calcium and vitamin D levels should be evaluated prior to the use of antiresorptive agents and, in case of deficiency, replacement should be carried out. Monitoring calcium and vitamin D during treatment is recommended[46].
- Osteonecrosis of the jaw: its incidence is variable, but an incidence of 1-2% has been described during the first year of treatment. Clinically, there may be pain, infection or ulcer. The event most related to its appearance is dentoalveolar surgery, which should be avoided during the use of antiresorptive agents. In case osteonecrosis of the jaw occurs, the patient should receive analgesia, mouthwashes, antibiotics and debridement[47].
- Atypical fractures: present in up to 1.8% of patients receiving denosumab or zoledronic acid. These fractures are reported as subtrochanteric and diaphyseal fractures of the femur, which can occur after minimal or no trauma[48,49].

Neutropenia associated with CDK4/6 inhibitors

Neutropenia is the most common hematological adverse event with the use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, due to a cytostatic effect on the cell cycle[50].

The risk of febrile neutropenia is considerably lower than that reported with chemotherapy. The use of colony-stimulating factors is not recommended for the treatment of neutropenia caused by CDK4/6 inhibitors, since discontinuation of the drug leads to a rapid recovery of the neutrophil count[51]. In case of significant and recurrent neutropenia, the management strategy is based on dose reduction.

Radiotherapy-induced toxicity

The use of 3D conformal radiotherapy (RT) with volume-based planning and strict adherence to the tolerance doses of each organ near the irradiation zone is mandatory. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group and other international collaborative groups have established tolerance limits for each organ and treatment volume. Patient education is essential[52,53].

Acute toxicity

- Fatigue. It is more severe halfway through treatment and remains so until 4-8 weeks after RT conclusion[54].
- Esophagitis. It may appear since the second week of treatment in patients with RT to the supraclavicular region and resolves completely 2-3 weeks after its conclusion[55].
- Dermatitis. Up to 95% of patients will develop grade 1 radiodermatitis. The degree of skin involvement depends on multiple factors. This complication is reversible and does not require treatment discontinuation, only appropriate management and close follow-up[56-58].

Subacute and chronic toxicity

Hypothyroidism

Up to 21% of patients may develop it during the first nine months after RT conclusion when the supraclavicular region is treated. Thyroid function tests should ideally be taken before starting RT and during the first six months after RT completion with semiannual follow-up for the ensuing five years[59].

Pneumonitis

Pulmonary toxicity occurs in 1-5% of patients with breast cancer and RT. Factors that increase the risk of

pneumonitis include concomitant use of chemotherapy, hormone therapy or targeted therapies, use of electrons, supraclavicular field, history of smoking and pulmonary diseases[60].

Cardiac toxicity and cardioprotection

Cardiac toxicity is the result of the interaction of various anticancer treatments and individual comorbidities. The spectrum of clinical presentations may include pericardial diseases, coronary artery disease, infarction, valvular heart disease, and heart rhythm irregularities. Early toxicity is subclinical, with identifiable changes six months after RT conclusion in patients with left breast cancer[61]. Late toxicity is characterized by coronary stenosis and ischemic heart disease with a latency period of 10 years. Emphasis is added on the use of modern techniques and strict adherence to dosimetric recommendations[62,63].

Lymphedema

In patients undergoing sentinel lymph node and chest wall RT, the addition of lymph node RT does not increase the risk of lymphedema. In contrast, this risk increases significantly in patients who undergo axillary dissection and RT to the chest wall or axillary dissection and RT to the chest wall and regional lymph nodes[64].

For more details about the management and approach for patients who develop lymphedema, this topic is extensively addressed in the rehabilitation section.

Radiation-induced cancer

There is an increase in the risk of second non-breast neoplasms associated with RT to the chest wall for breast cancer (relative risk [RR]: 1.12). The risk of suffering from lung cancer, esophageal cancer or radiation-induced sarcoma should be taken into account during RT planning (RR: 1.39, RR: 1.53 and RR: 2.53, respectively)[65].

Supportive and palliative care integration to the management of patients with advanced breast cancer

Introduction

Advances in breast cancer multidisciplinary management and early diagnosis have improved survival[66-68]. However, metastatic or recurrent breast cancer continues to be an incurable, although treatable disease[69]. In patient-centered oncology practice, in addition to antineoplastic treatments, it is important to consider physical, psychological and spiritual needs[70].

The support or palliative care priorities of people with advanced breast cancer vary throughout the disease. In the evolution of cancer, people can experience rapidly progressive symptom changes, or have stable symptoms for long periods (Fig. 1)[71]. The oncology staff must have the knowledge to provide basic supportive and palliative care, closely collaborating with palliative care specialists since diagnosis[70,72].

Palliative care is defined as active, holistic care of individuals across all ages with serious health-related suffering due to severe illness, and especially of those near the end of life. Its purpose is to improve the quality of life of patients, their families and their caregivers. It includes prevention, early identification, comprehensive assessment and management of physical issues, including pain and other distressing symptoms, psychological distress, spiritual distress and social needs[73].

Early integration of supportive and palliative care into the management of people with cancer can improve quality of life, symptom control, patient and family satisfaction, end-of-life care, survival, and costs of care[74]. The American Society of Clinical Oncology (ASCO), on its clinical practice guidelines, establishes that patients with advanced cancer should early receive supportive and palliative care (Table 1)[75] simultaneously with antineoplastic treatments; similarly, other societies have issued guidelines and recommendations for the incorporation of palliative care into the management of cancer patients[69,75,76].

Evaluation of palliative care needs

Systematic and structured evaluation of physical, psychological and psychiatric symptoms, cognitive alterations, the concept of disease and prognosis, care needs, existential concerns, as well as emotional and economic distress, is essential. Good symptom control improves the trust of people with cancer and their families.

The use of validated symptom assessment instruments helps to identify, treat and monitor symptoms. Self-assessment of symptoms using the different available scales is important, since doctors tend to underestimate their severity, which has an impact on the opportunity to establish a treatment that can contribute to improve both the symptom and quality of life.

In this model, it is essential to evaluate patient symptomatic complexity, in eight basic aspects:

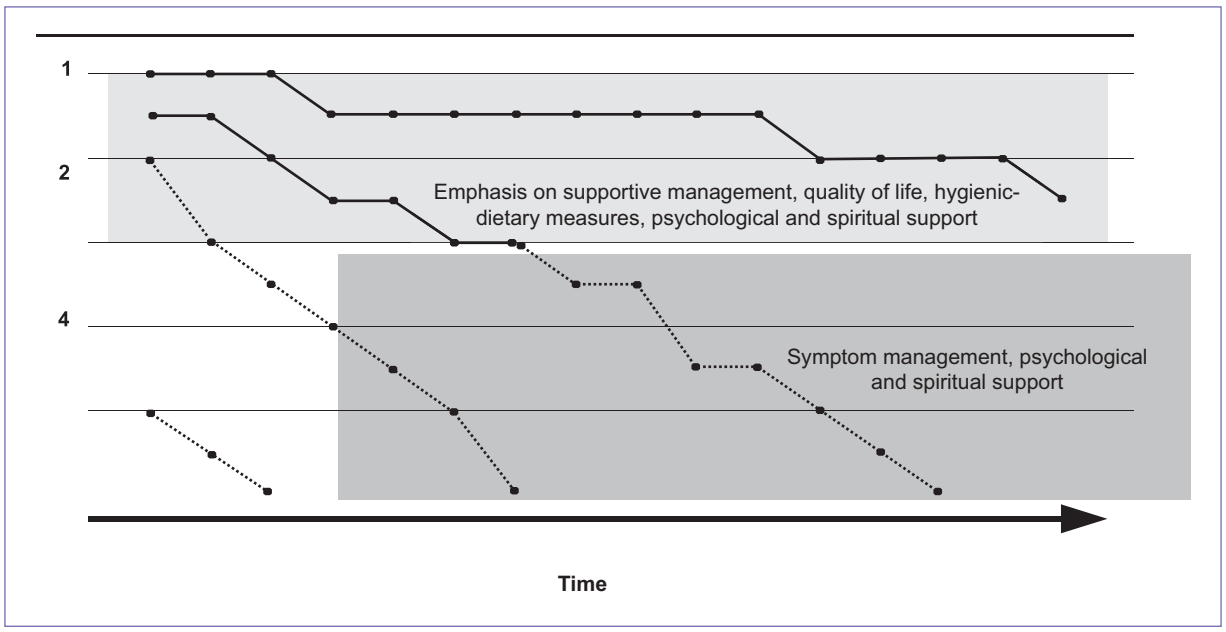

Figure 1. Possible trajectories in the evolution of metastatic breast cancer. 1) Slow evolution; 2) Gradual deterioration; 3) Rapid progression; 4) Poor prognosis at diagnosis. Symptom stability (solid line) or significant symptom burden (dashed line). *Modified from Kida et al.*[71]

Table 1. Integration of support and palliative care into standard cancer care

Supportive and palliative care should be started simultaneously with antineoplastic treatment. Referral to the supportive and palliative care department can be complemented with the oncologist's usual approach. This referral must include patient family members. (Evidence based on: benefits outweigh risks; quality of evidence, intermediate; strength of recommendation, strong.)
Essential components of supportive and palliative care services should include: – Ability to establish empathetic and committed relationships with patients and family members – Management of symptoms, distress and functional impairment (e.g., pain, dyspnea, fatigue, insomnia, anxiety, depression, etc.) – Strategies to evaluate and educate on the concept of disease and prognosis – Guidance for establishing treatment goals – Assessment and support to coping mechanisms and needs – Assistance with medical decision-making – Coordination with other specialists – Referral and counter-referral criteria
In patients newly diagnosed with advanced cancer, the expert panel suggests incorporating supportive and palliative care within the first 8 weeks after diagnosis. (Evidence based on: informal consensus; quality of evidence, intermediate; strength of recommendation, moderate.)
In outpatient oncology models, there should be programs and resources for providing supportive and palliative care on an outpatient basis to highly symptomatic patients or patients with unmet physical or psychosocial needs. (Evidence based on: the benefits outweigh the risks; quality of evidence, intermediate; strength of recommendation, moderate.)

Adapted from Dans et al.[76]

– Physical aspects of care (symptoms).
– Psychological and psychiatric aspects.
– Social aspects.
– Spiritual, religious and existential aspects.
– Cultural aspects of care.
– Care of the patient approaching the end of life.
– Ethical aspects of care.
– Discussion of end-of-life advanced planning and advance directives in accordance with current legislation.

Pain, fatigue, dyspnea, nausea, depression, anxiety and insomnia are the most common symptoms[77]. To obtain the best results according to the stage of the

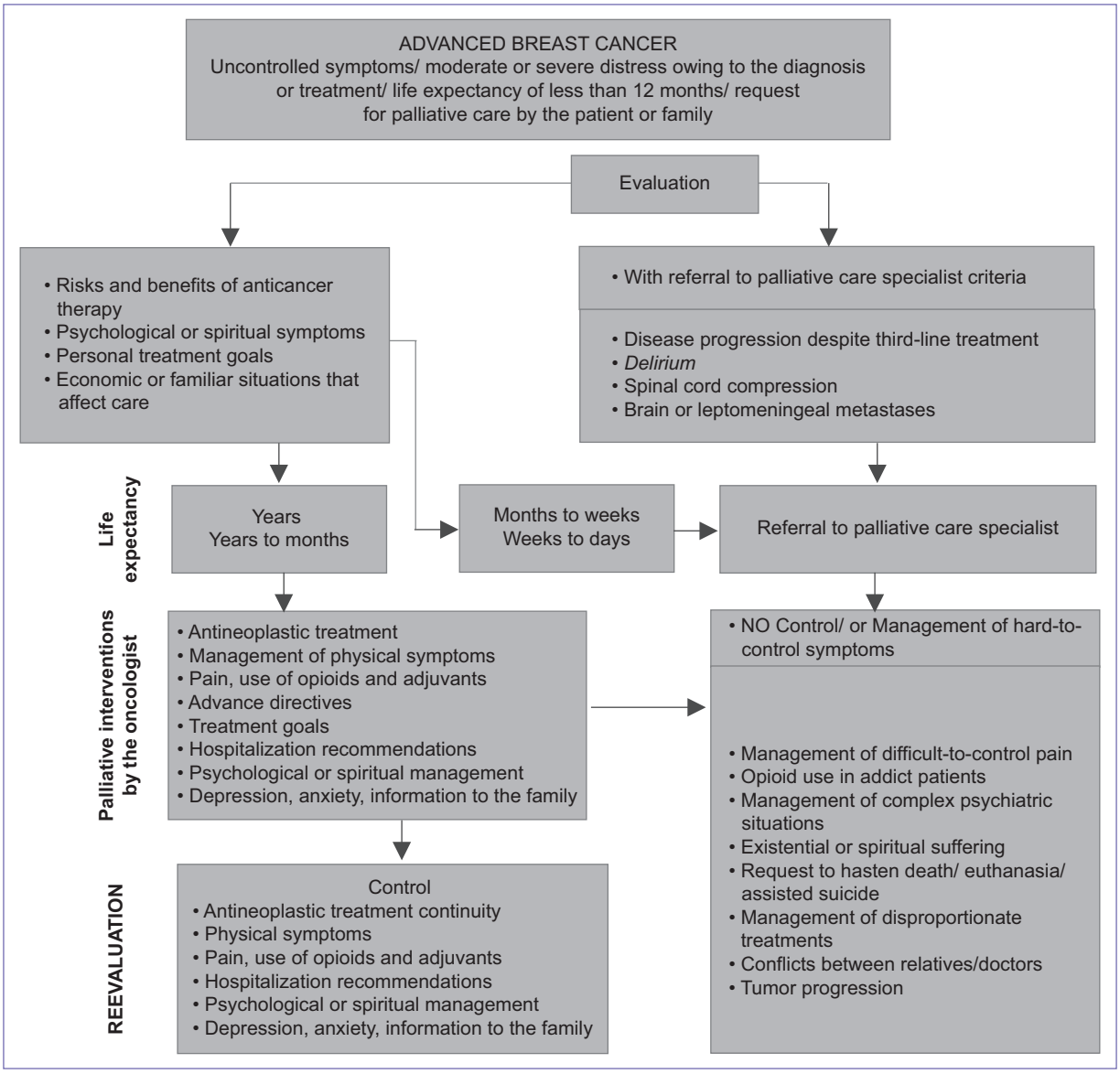

Figure 2. Role of the oncologist in palliative care.

disease and the symptom burden, doctors, paramedical personnel, patients and caregivers must be included in decision making[77]. One strategy that is frequently used in supportive and palliative care services is family meetings, in which medical aspects, treatment goals, identification of support networks and recommendations for the primary caregiver are covered.

This multiple-domain evaluation is not common in oncology consultation, which typically focus mainly on cancer treatment, the response to it, and medical complications, while symptoms and coping skills, and the systematic work carried out by supportive and palliative care services, are undervalued[70-72,78].

The discussion about comprehensive oncological-palliative evaluation should include a review of both risks and benefits of anticancer therapy and prognosis, in addition to ensuring that the patient and her family understand the seriousness of the disease. In this context, the oncologist's opinion on the benefit of referral to supportive and palliative care services must be considered (Fig. 2)[71,79].

Symptom management by the oncologist

The symptoms people with breast cancer experience are varied and change during the disease process, but

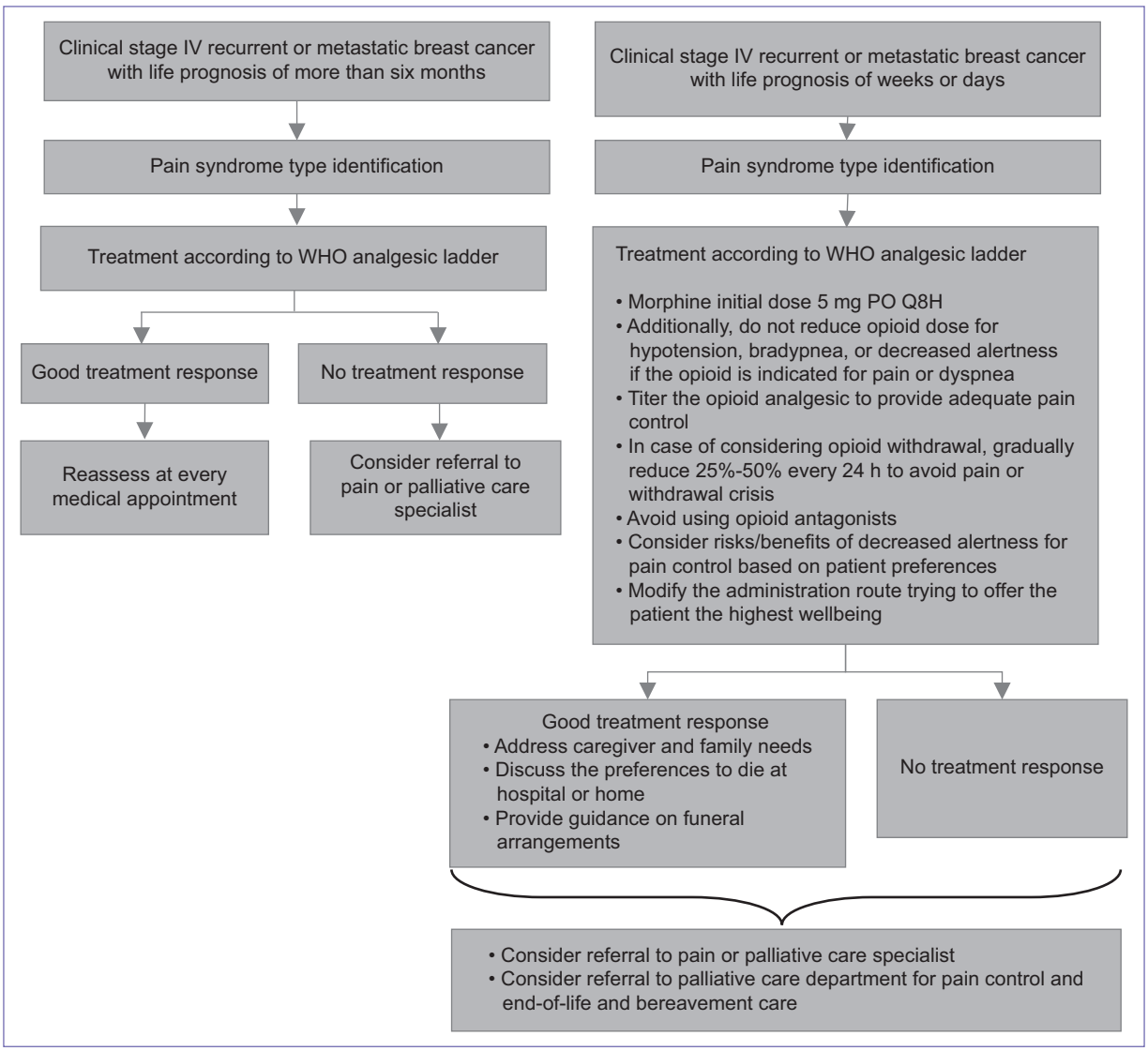

Figure 3. Pain management (*adapted from Levy et al.*[81]).
WHO: World Health Organization.

are accentuated at advanced stages and terminal phase. Pain, depression, anxiety, fatigue, dyspnea, insomnia, nausea and weight loss are common symptoms that cause increasing dependence and significantly contribute to increase patient suffering. Other symptoms associated with spinal cord compression, brain and bone metastases, lymphedema and anemia negatively impact quality of life as well[80,81].

Pain

Cancer pain is present in up to 70% of patients with advanced breast cancer due to disease progression[71,72,82]. Its management requires an approach that includes antitumor therapies, analgesic therapy and psychological care. The most common cause of pain is related to the presence of bone metastases and their complications. Other causes include pain due to chest wall infiltration, brachial plexopathy, and abdominal distension pain, among others.

It is important for the oncologist to become familiar with the pharmacological options for pain management, particularly with the use of strong opioids for the treatment of severe pain.

Figure 3 shows some recommendations for pain management. We emphasize the importance of early consulting pain and palliative care specialists to manage pain[72].

Recommendations for integrating patients with breast cancer and their caregivers into pain management:
- Provide clear, written medical instructions.
- Emphasize the importance of contacting the doctor in case of uncontrolled pain.
- Provide coping and self-management strategies.
- Identify patient expectations in terms of symptom control.
- Provide tools to avoid caregiver burnout.
- Include healthy life strategies, exercise and diet.

Dyspnea

Dyspnea is a common symptom, which consists of the subjective experience of respiratory discomfort, with qualitatively different sensations that vary in intensity. Treatment of underlying causes should be always considered (anemia, heart failure, asthma, lung infection, etc.). Opioids (oral morphine low doses) are the drug of choice for symptom palliation. Figure 4 describes the flow chart for its management[71,72,82].
- Provide breathing techniques.
- Condition physical area at home.
- Implement non-pharmacological measures.

Fatigue

The sensation of fatigue is common in patients receiving treatment and may persist in survivors. Evaluation of this symptom should rule out potentially treatable factors such as anemia, thyroid dysfunction, pain, depression, and insomnia.

Anorexia

Anorexia and weight loss are common in patients with advanced cancer and contribute to the feeling of tiredness, constituting an important part of family concerns. Megestrol acetate stimulates appetite, but does not improve quality of life or increase muscle mass, in addition to increasing the risk of edema and thromboembolic events. Corticosteroids improve appetite; however, prolonged use causes multiple side effects.

Delirium

Delirium is the most common neuropsychiatric complication in people with advanced breast cancer. It is characterized by an overall brain dysfunction of undetermined etiology, characterized by fluctuations in alertness, attention, thinking, perception, memory, psychomotor behavior, emotions, and sleep-wake cycle. Its etiology is multifactorial and can be hyperactive or hypoactive, with the latter being more frequent and underdiagnosed in patients with advanced cancer. There are different screening instruments for its evaluation, with the simplest being the confusion evaluation method.

Conclusion

The supportive and palliative symptomatic approach, in addition to improving quality of life, can help patients and caregivers have a realistic view of short- and long-term treatment goals. The symptoms described in this section do not cover all the problems present in people with advanced breast cancer; however, they give an overview of the supportive and palliative symptomatic approach for oncologists that will, at all times, focus on the person and his/her needs.

Genetics and breast cancer

Introduction

Approximately 20% of people with breast cancer have first or second degree relatives with a history of the same disease, which is considered a familial presentation. From 5 to 10% of cases are associated with a hereditary syndrome and 25 to 40% of these patients are younger than 35 years[83,84].

The genes related to hereditary breast cancer can be divided into those that confer high susceptibility (> 50%) (*BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PTEN*, *TP53*, *PALB2* and *STK11*) and moderate susceptibility (20 to 50%) (*ATM*, *BARD1*, *BRIP1*, *CHEK2*, *RAD51C*, *RAD51D* and *NBS1*)[84-86].

The prevalence of germline pathogenic variants (PV) of the *BRCA1* and *BRCA2* genes in the general population ranges from 1 in 50 to 1 in 800, depending on the ethnic group, and are responsible for 3 to 8% of all cases of breast cancer. These PVs explain up to 60% of breast cancer hereditary presentations and cause hereditary breast and ovarian cancer syndrome (HBOC)[85-88].

Women who are carriers of PVs in *BRCA1* have a cumulative risk at 80 years of up to 72% for developing breast cancer, and in the case of *BRCA2*, of up to 69%, while the cumulative risk for developing contralateral breast cancer is 40% and 26% for PV carriers in *BRCA1* and *BRCA2*, respectively. The cumulative risk at 80 years for developing ovarian cancer is 39-58% with PV in *BRCA1*, and 13-29% with PV in *BRCA2*[88,89].

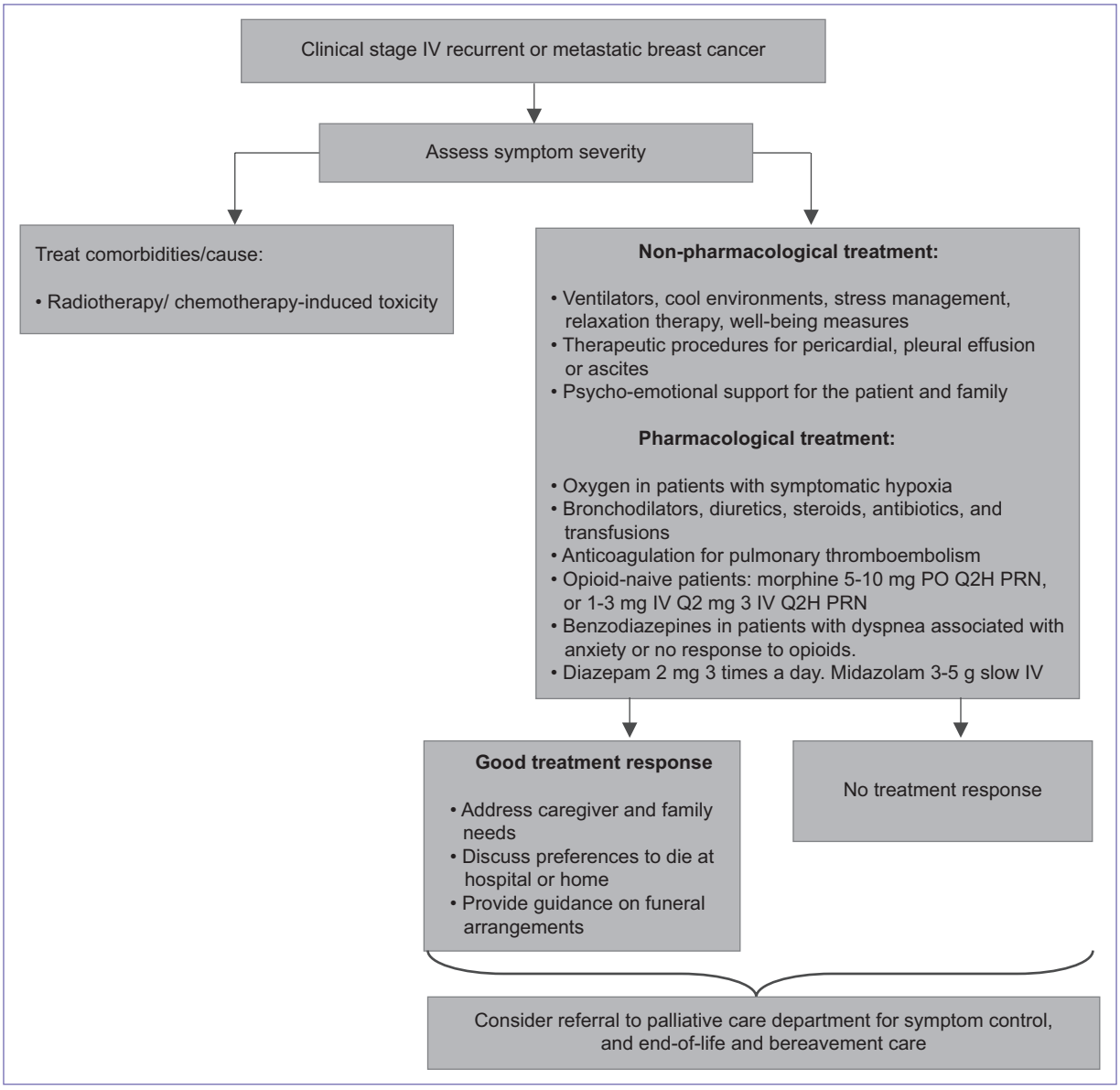

Figure 4. Management of dyspnea.
PRN: pro *re nata* (according to patient needs).

HBOC has an autosomal dominant inheritance pattern, which is why carriers' first-degree relatives have a 50% risk of inheriting it[86]. It is essential that health personnel identify patients at high risk of suffering from hereditary cancer, for referral to the multidisciplinary team, which must include an expert in cancer genetics for a comprehensive evaluation. The type of cancer and age at diagnosis in family members are key to the integration of a hereditary cancer syndrome. In some cases, there may be no family history of cancer, but this does not exclude the possibility for a hereditary cancer syndrome to exist. Molecular study is indicated in the population at risk (Table 2)[88,89].

Every patient who undergoes a germline molecular study should receive pre- and posttest counseling. An incomplete or inadequate assessment is associated with adverse effects, including negative emotional effects, incorrect surgical and follow-up measures, as well as erroneous interpretation of tests, in addition to economic consequences.

Multigene panels for hereditary cancer play an important role in the diagnosis of these patients; however, one of their limitations is the lack of knowledge about the risk level for many genes, lack of clinical guidelines and the high percentage of variants of uncertain clinical significance (without direct impact on clinical management), and they

Table 2. National Comprehensive Cancer Network criteria, version1.2023

Individuals with a family member who is carrier of a pathogenic or probably pathogenic variant (only the pathogenic variant known in the family will be searched)*
Individual with a history of partial or limited molecular testing
Diagnosis at any age: – Therapeutic indications (metastatic cancer, HER2–) (PARP inhibitors) – Triple-negative tumor – Multiple primary tumors (synchronous or metachronous) – Lobular breast cancer with personal or family history of diffuse gastric cancer – Male breast cancer – Ashkenazi Jewish ancestry. Family history: • ≥ 1 close blood relative with: breast cancer ≤ 50 years • Male breast cancer • Ovarian cancer • Pancreatic cancer • Metastatic prostate cancer, of high or very high risk ≥ 3 diagnoses of breast cancer in the patient and/or close blood relatives (1st, 2nd or 3rd degree)
≥ 2 close blood relatives with breast cancer or prostate cancer. Patient with a pathogenic variant identified on a somatic panel that could have implications if also identified on germline testing.

*Only indication for not to request a multigene panel.
Adapted from National Comprehensive Cancer Network, 2023[89].

should be indicated by health professionals trained in the subject, for a careful interpretation of results and consequent advice. Even in patients who meet clinical criteria for a hereditary cancer syndrome, the result of a panel can be unexpected[89,90]. This study is not a screening that can be offered to the general population.

Once a high/moderate risk PV carrier is identified, cascade testing should be offered to the family members at risk and according to the genealogy. In subjects younger than 18 years, genetic testing is generally not recommended when the results do not impact medical management, although it may be requested in cases where PVs in *TP53* or *NF1* are suspected[89].

The triple-negative tumor phenotype is mainly related to PVs in *BRCA 1*. Up to 20% of people with this tumor phenotype are carriers of germline PVs and, therefore, this characteristic is included among the clinical criteria[91,92].

In the Mexican population, 30-40% of cases diagnosed with HBOC may have a founder deletion in *BRCA1*, which consists of the loss of exons 9 to 12, which is why it should be deliberately sought[93].

Follow-up of patients who are carriers of a pathogenic variant of high-risk genes for developing breast cancer

It is recommended to start monthly breast self-examination at 18 years of age; annual or biannual clinical examination, as well as mammography and breast magnetic resonance imaging (MRI) starting at age 25[89]; however, the starting age may be according to the earliest age of presentation in the family. For women aged 76 years or older, management should be considered on an individual basis.

For people who were males at birth, chest self-examination starting at age 35, chest wall clinical examination every year, starting at age 35, and in those with gynecomastia, performing a mammogram every year starting at age 50 or 10 years before the first known male breast cancer in the family (whichever occurs first) is recommended.

Chemoprevention and other procedures in patients with pathogenic variants of genes that confer high risk for developing breast cancer

Chemoprevention with tamoxifen and aromatase inhibitors, risk-reducing mastectomy and the combination of mastectomy/oophorectomy-salpingectomy[83,88] should only be considered in a group of patients carefully selected by a multidisciplinary team, based on the objective risk for developing breast cancer, as well as patient personal wishes after genetic counseling.

Psycho-oncological aspects in breast cancer

Introduction

Psycho-oncology takes care of the psychological, social, cultural, anthropological, ethical-spiritual and

sexual aspects of cancer patients. Breast cancer diagnosis has a threatening meaning and appears as a premature risk of death. This effect will depend on a variety of factors such as age, socioeconomic situation, coping with the disease, and social and emotional support.

Psychological problems

One of the most prevalent psychological problems in patients with breast cancer is distress, defined by the National Comprehensive Cancer Network (NCCN) as "an unpleasant emotional experience of a psychologic (i.e., cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms and/or its treatment"[94].

Distress, depression and anxiety are the most prevalent mental health problems. These problems are associated with sleep disturbances, pain and fatigue, especially in patients with metastatic cancer[95]. Diagnosis and treatment of these pathologies is essential, as well as the type of coping, since they can influence hospital length of stay, self-care, treatment adherence and quality of life.

There may be effects on sexuality, depressive symptoms, anxiety, body image alterations, relationship problems, problems in the care of children, stigmatization and feelings of discrimination. People with breast cancer undergoing any preventive intervention are concerned about their future fertility and body image[96,97]. Symptoms of anxiety, decreased executive function, working memory alterations and concentration problems may occur in survivors, in comparison with people without a history of cancer.

Primary caregivers of this group of patients have been identified to experience psychosocial disorders such as anxiety, depression and overburden. Moreover, cancer has been reported to significantly impact couple relationships[98]. The most affected people are those who have poor problem-solving skills and marital difficulties prior to diagnosis[99].

Evaluation

Table 3 shows four brief tools, validated in Spanish, that can be used to identify patients and couples in need of psychosocial intervention.

Psychological therapy

Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is a therapeutic alternative for people with cancer. Its purpose is to modify cognitions and behaviors that complicate health problems through evidence-based techniques, seeking to correct irrational thinking patterns and beliefs associated with physical appearance, attractiveness and worth, and thus improve coping resources and promote emotional self-regulation.

The goals of CBT are divided into: a) approach to psychological problems associated with the diagnosis, treatment, follow-up period, and b) management of cancer treatment side effects such as nausea, vomiting, pain, insomnia, incontinence and sexual dysfunction.

There are different forms of professional psychological intervention, which can be classified as follows:

- Educational-informational interventions (counselling).
- Individual psychotherapeutic interventions (behavioral, cognitive, dynamic).
- Interventions mediated by group psychological processes[102].

CBT modifies the patterns that contribute to problems; it can also use conditioning and learning principles to modify problem behaviors. In addition, it improves the control of some symptoms, the emotional state related to specific situations and coping with the disease at its different phases[103].

Dignity therapy

In patients with advanced cancer and on palliative care, this therapeutic modality has shown positive effects on emotional well-being.

Self-care in breast cancer

Encouraging breast cancer self-care can improve esthetic, nutritional, reproductive and social outcomes. According to the Health Belief Model, four variables define health behaviors:

- Perceived susceptibility. The person must perceive him/herself as vulnerable to the disease.
- Perceived severity. The person must consider that the consequences of the disease are serious.
- Perceived benefits. The person must consider that health behavior will mitigate the threat posed by the disease.
- Perceived barriers. The person must consider that the negative aspects of preventive action are surmountable.

Psycho-oncologist intervention may constitute a key triggering moment for promoting these behaviors.

Table 3. Psycho-oncologic evaluation and treatment

Objective	Instrument	Treatment period	Therapeutic alternatives
Breast cancer patients			
To assess the level of emotional discomfort, needs, social support and coping	Distress thermometer	Diagnosis Treatment initiation	Information Psychoeducation Emotional validation Relaxation techniques
To assess the level of anxiety and depression symptoms	Hospital Anxiety and Depression Scale HADS	Treatment period Disease recurrence Palliative treatment	Cognitive-behavioral therapy, psychiatry and/or neurology Dignity therapy
Patient partners and informal primary caregivers			
To know the degree of adjustment (agreement) deemed by the partners within their relationship	Dyadic Adjustment Scale	Diagnosis Treatment initiation Treatment period	Information Psychoeducation Cognitive-behavioral therapy
To evaluate the level of overburden associated with patient care	Zarit Burden Interview Scale	Treatment period Palliative treatment	Cognitive-behavioral therapy

Ninth version: Alternatives for psychological evaluation and treatment of the cancer patient.
Adapted from Galindo et al., *2015*[100] *and Galindo-Vázquez* et al., *2015*[101].

Physical rehabilitation of the patient with breast cancer

Introduction

Advances in treatments and increased survival of breast cancer patients demand for rehabilitation methods to be increasingly effective in order to achieve a better quality of life. After treatment, complications may occur, some of which are exclusively related to primary tumors, others to axillary lymph node dissection, to lymphatic vessels recanalization,[104] to cancer treatment (chemotherapy or RT), and/or to infectious processes.

Physical rehabilitation has three stages:

- Preventive: it reduces the impact and severity of expected disabilities.
- Restorative: it seeks to improve and/or return to the premorbid status without significant disabilities.
- Support: it seeks to provide the tools to overcome difficulties, having a feeling of control and choices. It tries to adapt the person to the circumstances that have changed with the disease and its treatment.

Lymphedema

People treated with axillary dissection are at risk for lymphedema, which is associated with the number of lymph nodes removed and RT use of. Overweight and obesity increase the risk and negatively impact treatment results[105-108]. It is essential for rehabilitation to be timely implemented[109].

Lymphedema complications include[110]:

- Recurrent infections (lymphangitis, erysipelas, cellulitis).
- Body image disorder.
- Situational and chronic low self-esteem.
- Impaired social interaction.
- Personal identity disorder.
- Intolerance to activity.
- Self-care deficit.

Lymphedema stages

- Stage 0: latency.
  - No clinical data consistent with lymphedema.
- Stage I: reversible.
  - Evident volume increase.
  - Usually, limb elevation reduces edema, but does not stop its progression.
- Stage II: spontaneously irreversible.
  - Significantly increased limb volume.
  - Lymphatic fibrosis (areas of higher stagnation).
  - Limb elevation does not reduce edema.
- Stage III: lymphostatic.
  - The limb significantly increases in volume.
  - Lymphatic fibrosis (areas of higher stagnation)
  - Extremities more prone to infections.
  - Physical disability.

Management of lymphedema and shoulder joint mobility in patients treated with curative intent

The person must know about the risk of developing lymphedema and its consequences, and that this risk decreases with rehabilitation. Training should be provided on scar massage and fascia mobilization once the stitches and drains are removed. This is effective for reducing adhesions in deep planes, improving flexibility and mobility, reducing the thickness of the scar and surrounding healthy skin, and for preventing pectoralis major muscle spasm, frozen shoulder, and adhesive capsulitis.

Scapulohumeral joint mobilization should start since the first postoperative day: shoulder flexion and extension with the elbow flexed at 90º. Shoulder abduction movements should not be made for seven days, since it takes that time for axillary lymphatic capillaries to be reestablished.

Starting on the eighth day, movement of the arm should be initiated with passive exercises (with the help of another person) of shoulder flexion, abduction and rotation. Once the full range of motion is achieved, an active exercise program should be started in order to keep the lymphatic system permeable, as well as a shoulder muscle stretching program to maintain adequate muscle dynamics. In case of having a catheter port, exercises should be adapted to prevent future injuries.

In patients diagnosed with lymphedema, the following should be avoided:

- Lifting heavy objects. Progression can be addressed with physical work and with guidance of a professional.
- Sleeping on the affected arm.
- Weight gain.
- Applying thermotherapy or cryotherapy.
- Acupuncture on the affected arm.
- Use of diuretics, except if medically indicated.

The medical compression garment for risk reduction (20-30 mm Hg) must be indicated by a specialist in the treatment of lymphedema, who should provide the corresponding instructions for traveling, physical activity and carrying out strenuous activities at home and workplace.

The treatment indicated for lymphedema is complex decongestive therapy (CDT)[111,112] or combined physical therapy[113]. Although lymphedema has no cure, this treatment can reduce and control it.

The four components of CDT are:

- Care of the nails and skin of the compromised quadrant.
- Manual lymphatic drainage (MLD).
- Compression therapy with short traction or Circaid® bandages and medical compression garments.
- Myolymphokinetic exercises[113].

This non-invasive therapy in most cases restores patient control over their lymphedema and reincorporates them to a functional life. A patient who already has lymphedema should receive this treatment before wearing a compression sleeve. The use of a sleeve without treatment causes hand edema and can make patients and doctors think that the sleeve does not work.

Neuromuscular bandage with an appropriate technique and respecting the lymphatic anatomy is placed with the purpose to stimulate lymphatic drainage (CDT); thanks to the elasticity and S-shaped adhesive of the bandage, it physiologically stimulates the afferent receptors, exerting a change in interstitial pressure, thus favorably complementing the intervention[114].

Sequential pressotherapy with a working pressure of between 20 and 40 mm Hg and of 20 to 45-minute duration is a complementary part of MLD.

Physical exercise can help control musculoskeletal and joint mobility symptoms. Physical activity, together with the use of analgesics, aims at helping the cancer patient to improve functionality and restore the sense of control over pain[115]. Lymphatic drainage, exercise, and compression garments help reduce local levels of inflammatory mediators, which are often associated with edema and pain[116], body image alteration and decreased libido[117].

Physical rehabilitation intervention in patients with advanced disease

People with advanced-stage breast cancer can have edema, decreased mobility, and skin ulcers. This makes daily living activities difficult, generating loss of independence and deterioration of the quality of life of the patient and her caregivers[118,119].

The purpose of rehabilitation therapy in patients with advanced disease is, therefore, to maintain self-sufficiency for as long as possible, preserving mobility and muscle strength and reducing pain. This includes the use of complex decongestive therapy or combined physical treatment. In addition, it will be important to train the primary caregiver in techniques to maintain, improve or reduce disability.

Conclusions

In conjunction with cancer treatment, it is necessary to implement multidisciplinary measures aimed at improving the quality of life and global outcomes of patients with breast cancer. Inclusion of experts in rehabilitation,

psychology, palliative care and genetics is an essential part of the team for the treatment of breast cancer, and this edition of the Mexican Breast Cancer Consensus puts special emphasis on their early inclusion and on evidence-based decision-making.

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Conflict of interests

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been carried out on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article. In addition, the authors have recognized and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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