Belgian Society of Medical Oncology (BSMO) task force on breast cancer survivorship

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Advances in screening, diagnostic procedures, surgical techniques, knowledge about molecular pathways and targets, and new treatment options have substantially improved the outcome of breast cancer patients. Care for breast cancer survivors has thus become an essential part of care for breast cancer patients. Therefore, the Belgian Society of Medical Oncology set-up a task force charged with developing guidance on issues important for breast cancer patients who have completed their primary treatment.

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Introduction

Breast cancer (BC) is a major health issue. In the United States, it is estimated to affect one in eight women during their lifetime, and it is the second leading cause of cancer death in women.[1] In Belgium, BC is both the most frequent malignancy and the most frequent cause of cancer death in women. In 2008, BC accounted for 16 % of all newly diagnosed malignant tumours (N=9,697; data from Belgian Cancer Registry).[2]

The members of the task force met in April 2012. Several issues relevant to the follow-up of breast cancer survivors (BCS) were selected and assigned to each of the members for review. All members of the task force were involved in the writing of the guidelines and agree with its content. Medical oncologists with a special interest in BC were also consulted and reviewed this document.

Recommendations for follow-up after breast cancer surgery

The follow-up of BCS has been a matter of debate for years. A minimal follow-up, including regular medical consultations and yearly mammography, is recommended by most international guidelines.[3-6] These recommendations derive mainly from two prospective, randomised controlled trials (RCTs) carried out in the 1980s. These studies combined data from over 2,000 patients who had received treatment for primary BC and compared an intensive follow-up schedule to a clinical one.[7-9] The intensive follow-up schedule consisted of a periodic physical examination and annual mammogram as well as additional tests (e.g. planned bones scan, chest x-ray, blood draws and abdominal ultrasonography). Both studies concluded that there was no survival advantage for the intensive surveillance schedule. A meta-analysis including these two trials reached the same conclusion.[10] The same meta-analysis included two small RCTs: one study comparing patients followed by trained general practitioners to patients followed by hospital-based specialists and the other study investigating the acceptability of a follow-up with less frequent visits, namely restricted to the time of mammogram.[11,12] The former trial demonstrated that general practice follow-up was feasible and satisfactory for patients, and the latter trial showed that follow-up with less frequent visits is also well accepted by BCS.

It should be emphasised that these studies were conducted more than 20 years ago and that patients were

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not treated in the past as they would be today. The critical difference is that BC is nowadays recognised to be a heterogeneous group of malignancies with distinct molecular subtypes and outcomes.[13,14] The different subtypes influence adjuvant treatment decision-making, but they are not currently taken into consideration to determine the follow-up of BCS.

However, these subtypes affect patterns of relapse. Patients with triple-negative (TN) and HER-2 positive BC tend to relapse early, with the vast majority of relapses occurring within the first five years.[15,16] Patients with luminal-A tumours have the best outcomes, but local and distant relapses may occur up to 15 years after BC diagnosis. This is also true for patients with luminal-B tumours.[15,16]

The site of distant metastasis is also influenced by molecular subtypes and should therefore be considered in the follow-up strategy.[17] For example, cerebral metastases tend to occur more frequently in TN and HER2-positive BC than in other subgroups.[18]

Early detection of recurrences can be achieved by using laboratory tests or imaging techniques. Although radiological and/or serological testing can detect disseminated disease in asymptomatic patients, improved overall survival has not been demonstrated.[19] On the contrary, this approach negatively affects quality of life by introducing anxiety and inconvenience to asymptomatic patients.

This occurs frequently when the CA15-3 test is used. Results can be elevated without confirmation of metastatic disease and this leads to the dilemma of whether to treat or not. Furthermore, the CA15-3 test has low sensitivity for detecting metastatic disease, and the marker is usually not elevated in cases of loco-regional relapse and contralateral new BC.[19]

Because most recurrences are detected by patients themselves in the interval between follow-up appointments, and since there is no evidence from well-designed RCTs of either a survival or quality of life benefit when asymptomatic recurrences are detected early, screening with laboratory testing or imaging to detect distant relapse is not indicated and is discouraged by most experts and guidelines.[8,20-22]

Currently, the only test that is unanimously accepted is mammogram because it is more sensitive in detecting intra-mammary relapses than clinical examination alone.[23,24] Though this is a current practice worldwide, there is a lack of evidence from prospective RCTs showing a survival benefit. Retrospective studies have demonstrated that early detection of a local relapse or a contralateral BC with mammogram reduces the BC mortality rate.[25] Local relapses occur mostly within two to five years after initial treatment, but second primary tumours may occur many years later. Therefore long-term surveillance is mandatory for all patients.[26]

Indeed, BCS, especially women with a strong family history of BC, are at high risk of a second primary tumour in the conserved and/or contralateral breast.[27] Despite the high prevalence, one study demonstrated that surveillance mammogram in this patient population was less likely to detect secondary early-stage BC and actually correlated with a higher interval cancer rate (cancer diagnosed between the screening exams) than in a population of similar women without a personal history of BC.[28] Indeed, a recent study reported that roughly one-third of recurrences and second primaries are diagnosed at the interval between screening exams.[29]

Contrast-enhanced magnetic resonance imaging (MRI) of the breast is better able to rule out cancer than mammogram in several risks subgroups, particularly (1) women with an inherited predisposition to BC;[30-32] (2) patients with breast reconstruction or prosthetic implants;[33] and (3) patients with dense parenchyma[34] or lobular cancers.[35] However, MRI is not recommended for routine BC surveillance by most expert groups because it is expensive and associated with a high rate of false positive results, leading to unnecessary breast biopsies. [32,36]

Taking these elements into consideration, the BSMO task force recommends the following-up surveillance of BCS:

1. Regular medical consultations, which are used to identify symptoms or signs of local, regional or distant relapse, in order to plan complementary exams as indicated. This requires taking an extensive history and conducting a careful physical examination. Follow-up visits are thus "symptom driven" and not organised as "all-inclusive packages," except for the mammogram. Annual surveillance mammogram and ultrasound is recommended starting one year after the initial diagnosis and at least six months after radiation therapy.[22]
2. Blood tests may be ordered once a year in order to check lipids, glycaemia, thyroid function, and vitamin D, though this is not evidence-based. Nor there is an argument to routinely screen for serum tumour marker CA15-3 in asymptomatic patients; nevertheless, this appears to be a common practice worldwide.
3. Regular gynaecologic follow-up is recommended for all women treated for BC;[22] for women on tamoxifen who experience vaginal bleeding (not as consequence of return of menses), uterine ultrasonography and

Table 1. Task force recommendations according to BC subtypes

Intervention	Luminal A	Luminal B	HER 2	TN
Consultation	FU years 1-2: Q 4 months FU years 3-5: Q 6 months FU > years 5: Q 1 year	FU years 1-2: Q 3 months FU years 3-5: Q 6 months FU > years 5: Q 1 year		
History, physical exam *(incl. weight, blood pressure)*	Oncologist, radiotherapist, breast surgeon (alternating turns)			
Laboratory tests *(complete blood count, biochemistry, glucose; FSH, LH, oestrogen in pre-/peri-menopausal pts)*	Yearly			
Imaging low risk	Yearly Mammogram and ultrasound			
Imaging high risk *(implants, BRCA, lobular)*	Yearly mammogram and ultrasound (+/- MRI) BRCA: every 6 months (alternating MRI and mammogram and ultrasound)			
Bone densitometry *(Risk factors or aromatase inhibitor)*	At baseline and every 2 years			Not applicable
Tumour markers	Not recommended			
Other laboratory tests *(incl. vit D, thyroid function)*	At physician's discretion No formal recommendations			
Other imaging *(chest X-ray, bone scintigraphy, abdominal ultrasound)*	According to physician's assessment "Symptom driven" follow-up			
LVEF if anthracyclines or trastuzumab	Not applicable	Every 3 months while on therapy; every 6 months up to 2 years after treatment cessation if possible*		

*PE: physical examination; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging. *in case of anthracyclines, consider perform LVEF assessment when cumlative dose of epirubicin >300-400 mg/m² or doxorubicin >180-240 mg/m².*

endometrial biopsy are mandatory.[37]

4. Surveillance intervals and complementary exams should be adapted according to the BC subtypes, as outlined in *Table 1*.

Recommendations for populations at high risk of breast cancer

The following recommendations apply to patients with a known BRCA1 or BRCA2 gene mutation or to first-degree relatives (parents, brothers, sisters, or children) of patients with such mutations, and who have not had genetic testing themselves.

Annual follow-up

The BSMO task force recommends follow-up for women at high risk of developing BC to start at the age of 25 years or earlier if there is a family history of early-onset BC. This annual follow-up should include clinical breast examination (CBE) and imaging of the breast (mammogram plus ultrasound) alternating with breast MRI every six months.

MRI has been shown to be a particularly sensitive screening method in high-risk populations. The MARIBS study, which compared screening with breast MRI in addition to mammogram, showed that breast MRI was more sensitive than mammogram for ruling out malignant lesions (77% *vs.* 40%, respectively).[30] The sensitivity of combining both methods was 94%. In the EVA trial, breast MRI had the highest positive predictive value (48% compared with 39% for mammogram and 36% for ultrasound). Furthermore, BC was diagnosed significantly more often by MRI than by mammogram and/or ultrasound.[38] Finally, it has been demonstrated that adding breast MRI to conventional tests (mammo-

Table 2. Summary of recommendations for follow-up in high-risk patients.

Annual follow up as of 25 years of age:
Clinical breast examination
6-monthly breast imaging: alternating ultrasound and gadolinium enhanced MRI
Mammogram from age of 30
Prophylactic bilateral salpingo-oophorectomy:
After completion of childbearing
BRCA1: at age < 40 / BRCA2: age 40 to50
Prophylactic bilateral mastectomy (PBM):
Evaluation on a case-by-case basis
Consider psychological aspects
Annual follow-up with thoracic-wall and axillary ultrasound
Breast MRI (if implants)
Male (BRCA2 mainly):
Annual PSA and digital rectal exam from the age of 40
Education for breast self-examination
Baseline mammogram if gynecomastia or parenchyma/glandular breast density on ultrasound
Other for BRCA2 carriers:
Annual skin examinations by specialist

gram/ultrasound and clinical breast examination) provides a highly sensitive screening strategy, better than either method alone, for detecting early BC in young women with high-risk of developing the disease (sensitivity range 93-100%).[39]

Prophylactic bilateral salpingo-oophorectomy

The risk of gynaecologic cancer (ovarian and fallopian tube) is 10 to 40 times more elevated in patients with BRCA1 or BRCA2 mutations.[40,41] The absence of reliable methods for early detection of ovarian cancer, and the poor prognosis associated with it when identified in an advanced stage, supports performing a bilateral risk-reduction salpingo-oophorectomy (RRSO) in high-risk groups.

RRSO is associated with a significant reduction of more than 80% of BRCA-associated gynaecologic cancers (HR[95%CI]: 0.21[0.12-0.39]), and 50% of BRCA-associated BC (HR[95%CI]: 0.49[0.37-0.65]).[42] In terms of mortality, a prospective study showed that RRSO correlates with a 76% reduction in gynaecologic cancer-specific mortality, a 56% reduction in BC-specific mortality, and a 60% reduction in overall mortality.[43] Notwithstanding these encouraging results, we must remain vigilant because even after RRSO there is a substantial residual cumulative risk for peritoneal cancer, estimated at up to 4%, 20 years after RRSO.[44,45]

There is no 'appropriate' timing for RRSO; it is generally considered after the completion of childbearing or determined according to the earliest age of ovarian cancer diagnosed in the family. In the absence of a family history of gynaecologic cancer, the incidence of ovarian cancer differs between BRCA1 and BRCA2 carriers. The former have a gynaecologic cancer risk of 2% to 3% when they are in their late 30s, whereas the latter have a similar risk in their 50s. Therefore, BRCA1 carriers should consider RRSO by their late 30s to early 40s, while BRCA2 carriers could wait until their mid-40s.[46] However, early RRSO may be considered for BC risk reduction.

Physicians need to give realistic and balanced information about both the benefits and possible drawbacks of this preventive strategy, including information about ovarian function and menopause. Because RRSO induces an abrupt, surgically induced early menopause, it is important to consider the increased risk for cardiovascular diseases, bone health and quality of life (vasomotor symptoms and possible cognitive alterations).

Prophylactic mastectomy

In high-risk populations, prophylactic bilateral mastectomy (PBM) decreases the risk of BC to below that of the general population.[47] The risk of BC is reduced by approximately 95% in women with prior or concurrent bilateral prophylactic oophorectomy and by approximately 90% in women with intact ovaries. Nevertheless,

no impact on overall survival has been demonstrated.
A large cohort study including women with a history of primary BC showed that these women had a high risk – up to 40% – of developing a contralateral disease at 10 years.[48] The risk is increased in BRCA1 carriers and in women who had their first BC at a young age. This risk can be alleviated with RRSO, and PBM is also highly effective.[49]
There is no consensus for follow-up after PBM, though we recommend an annual (or biannual) breast examination, an annual ultrasound of the thoracic wall, axillary regions and, axillary regions and, depen-ding on the type of reconstruction and plastic surgeon's judgment, a breast MRI to exclude rupture of the prosthesis.
In conclusion, the decision whether or not to perform PBM must be discussed with women at a high risk of having BC. The decision must be evaluated on a case-by-case basis by an expert team, including a plastic surgeon and a genetic counsellor. The patient should take into account the risks and benefits of the surgery (e.g., necrosis, erectile sensibility of the nipple) and its potential psychological effects. Immediate or delayed reconstruction of the breast should also be discussed.

Male carriers

Male BRCA carriers have an increased risk of breast and prostate cancer. The susceptibility appears to be higher for men with BRCA2 mutations.[50] Indeed, BRCA2 carriers have a 4.7-fold increased risk of developing primary prostate cancer (1.8-fold increased risk for BRCA1)[51,52] and a lifetime BC risk of 6.8% (1.2% for BRCA1 and 0.06% for the general population).[53]
We recommend training patients to do a monthly self-examination of the breast up to the age of 35 and have a baseline mammogram at age of 40 if there is gynaecomastia or parenchyma/glandular breast density on ultrasound. We also recommend annual prostate specific antigen (PSA) screening and a digital rectal exam from the age of 40.

Others

In BRCA2 carriers, the incidence of melanoma (and intraocular melanoma) is 2.6 times higher (relative risk (RR) 2.6; 95% CI 1.3-5.2), particularly in carriers younger than 65 (RR 3.2; 95% CI 1.6-5.8). Therefore, we recommend regular thorough skin examination by a specialist.[50] However, there is no direct evidence that this type of screening will reduce mortality. A summary of recommendations for follow-up of high risk patients is depicted in *table 2*.

Fertility issues in patients with breast cancer

Chemotherapy may affect the future fertility of young patients with BC. This appears to depend on the age of the patient and the use of cyclophosphamide-based regimens.[54] There is a lack of prospective data to estimate the absolute effect of the different regimens on ovarian function. However, available data on chemotherapy-induced amenorrhea suggest that around 25% to 30% below the age of 40, and 45% to 70% of patients above 40 will develop permanent amenorrhea, depending on the chemotherapy regimen used.[55] Given that the ovarian reserve of women who resume menses after chemotherapy are compromised,[56] the absolute effect of chemotherapy on ovarian function and diminished subsequent fertility is expected to be even higher.
Pregnancy following BC does not appear to have a detrimental effect on BC outcome.[57] This is also true of patients with a history of an endocrine sensitive disease according to the results of a large multicentre study that was recently reported.[58] This study included 333 patients with BC who became pregnant following diagnosis and 874 who did not but who had the same age, stage, oestrogen receptor (ER) status and were treated similarly. Nearly 60% of patients enrolled in this study had ER-positive BC. At a median follow-up of five years following pregnancy, patients who had become pregnant following ER-positive BC did not have an increased risk of BC recurrence (HR 0.91; 95% CI 0.67-1.24; p=0.55). In the same study, induced abortion did not show to have any effect on BC outcome independent of ER status, and hence abortion should not be promoted for therapeutic purposes
To date, there are no data on the safety of the early interruption of hormonal therapy. Women should therefore be advised to complete their adjuvant therapy before considering pregnancy. Available evidence shows that pregnancy outcome in BCS who have received prior chemotherapy, hormonal therapy, and/or trastuzumab is comparable to that of the general population, which is rather reassuring.[59-61] Taken together, pregnancy should not be discouraged in BCS.
Young BC patients who wish to bear children should undergo fertility counselling prior to the initiation of adjuvant therapy.[62] Available options include embryo or oocyte cryopreservation, in addition to ovarian tissue cryopreservation, the latter being highly investigational at this time. The former two methods require ovarian hyperstimulation, however, which is associated with a transient increase in estradiol levels (for around 10 days)

Table 3. LEVF assessment in asymptomatic patients receiving anthracyclines and/or trastuzumab

	LVEF assessment in asymptomatic patients	
	During therapy	**During follow-up**
Anthracycline-based CT (Doxorubicin or epirubicin)	Prior, during and at the end of chemotherapy*	At 6 months and then yearly for 2 to 3 years if possible
Trastuzumab	Every 3 months while on therapy	Every 6 months up to 2 years after treatment cessation if possible

*LVEF: left ventricular ejections fraction; CT: chemotherapy. *in case of anthracyclines, consider perform LVEF assessment when cumlative dose of epirubicin >300-400 mg/m² or doxorubicin >180-240 mg/m².*

and could result in delaying the initiation of adjuvant therapy.[63] Currently, there are ovarian stimulation protocols associated with relatively low estradiol peaks, and they appear to be safe in patients with BC.[63-66]

The use of luteinizing hormone-releasing hormone (LHRH) agonists with chemotherapy should not be regarded as a method to preserve fertility. Data on the effect of LHRH agonists on reducing chemotherapy-induced amenorrhea are rather contradictory,[67-69] and certainly more data are required to fully understand their impact on ovarian function.

Summary of recommendations for fertility issues

1. Pregnancy in BCS does not increase the risk of BC recurrence irrespective of ER-status
2. Inducing abortion in BCS does not impact BC prognosis and hence should not be promoted for therapeutic purposes
3. Short-term foetal outcome in BCS who subsequently become pregnant is highly comparable to that of the general population
4. Patients should be advised to complete adequate adjuvant therapy prior to considering pregnancy
5. Fertility counselling is strongly recommended prior to commencing adjuvant therapy. Current established methods are either embryo or oocyte cryopreservation. Consultation with fertility specialists is highly encouraged and should be considered within the context of the multidisciplinary management of young BC patients.

Cardiac toxicity with adjuvant therapies

Cardiac toxicity is a potential long-term complication of several anticancer therapies, including chemotherapy, radiotherapy and targeted agents. Some anticancer drugs, such as anthracyclines, may cause potentially irreversible cardiac dysfunction. Other drugs, such as trastuzumab, are considered less cardiotoxic and better tolerated by patients than classic chemotherapeutic agents. However, several drugs may cause other cardiovascular effects, such as hypertension, QTc prolongation, and arrhythmias, and they are well described in the recently published European Society for Medical Oncology (ESMO) guidelines.[70] The European Society of Cardiology also published its guidelines a few years ago.[71]

Risk factors for developing cardiac toxicity in patients treated with anthracyclines include the following: total cumulative dose; intravenous bolus administration (rather than continuous infusion); history of prior chest irradiation; the use of other concomitant agents known to have cardiotoxic effects (e.g. cyclophosphamide, trastuzumab, and paclitaxel); female gender; underlying cardiovascular disease; increased age; increased length of time since completion of chemotherapy; and increase in cardiac biomarkers, such as troponins and natriuretic peptides, during and after administration (if tested).[72-76]

The risk of clinical cardiotoxicity increases with cumulative dose. Studies evaluating cumulative probability of doxorubicin-induced heart failure reported rates in the range of 3% to 5% with 400 mg/m², 7% to 26% at 550 mg/m², and 18% to 48% at 700 mg/m². The recommended maximum lifetime cumulative dose is 400 to 550 mg/m² for doxorubicin and up to 720 mg/m² for epirubicin.

Generally, anthracyclines cause type I cardiotoxicity, which is dose-dependent, irreversible and normally associated with biopsy changes. By contrast, trastuzumab causes type II cardiotoxicity, which is not dose-dependent, largely reversible and does not produce ultrastructural changes on histological examination.[77,78] The cardiotoxicity caused by trastuzumab remains low at a median follow-up of 8 years. Occuring mostly during trastuzumab administration, it is largely reversible when trastuzumab is stopped.[79,80]

Screening and evaluation during anticancer therapy can be done by LVEF assessment using echocardiography,

Table 4. Management of trastuzumab cardiotoxicity (reprinted with permission from ESMO).[70]

• Management of trastuzumab-related cardiotoxicity has two distinct aspects: withdrawal of trastuzumab therapy and treatment of cardiac dysfunction.
• The "stopping/restarting" rules used in the adjuvant trials were effective and are recommended, with some modifications regarding recommendations for a cardiology consult or treatment of cardiac dysfunction (or both) when appropriate.
• Symptomatic left ventricular dysfunction must be treated with heart failure treatment: All patients with heart failure and a LVEF below 40% should be treated with an ACE inhibitor in combination with a beta-blocker unless a specific contraindication exists (class I, level A evidence). Some members of the panel also felt that, to prevent further degradation of LVEF or the development of clinical heart failure, an ACE inhibitor should be considered if the patient's LVEF is between 40% and 50%.
• **Asymptomatic left ventricular dysfunction should be treated:** ACE inhibitors should be used in all asymptomatic patients with left ventricular dysfunction and an ejection fraction below 40% (class I, level A evidence for ejection fraction below 35%; class I, level B for ejection fraction between 35% and 40%). Also, an ACE inhibitor should be considered if LVEF is below 50%. Beta-blockers should be considered in all patients with asymptomatic left ventricular dysfunction and a LVEF below 40% (if prior myocardial infarction, class I, level B evidence; if no myocardial infarction, class II, level C).

MUGA scan or cardiac MRI. The use of cardiac biomarkers (e.g., BNP, high sensitivity troponin) remains investigational and is not routinely recommended to all patients. However, cardiac biomarkers may be applied in some cases where treatment cessation is being considered or in patients at high-risk of developing cardiac toxicity. *Table 3* summarizes the recommendations of the BSMO task force for cardiac assessment in patients treated with anthracyclines and/or trastuzumab therapy. Patients experiencing LVEF decrease or cardiac dysfunction during therapy should be followed in collaboration with a cardiologist, and the interval and type of assessment should be jointly discussed and agreed upon. However, patients will be assessed differently in case of cardiac toxicity while on treatment (e.g., anthracyclines and/or trastuzumab). The management of patients experiencing trastuzumab-induced cardiotoxcity is summarized in *table 4*.[70]

Bone health after breast cancer

BC therapies may result in bone loss leading to osteoporosis and fractures. Therefore, addressing issues related to bone health is paramount for BCS. The Women's Health Initiative Observational Study reported that BCS have significantly lower total body bone mineral density (BMD) value and total hip BMD value,[81] as well as an increased risk of clinical vertebral fractures.[82]

The mechanism by which cancer therapy causes bone loss is primarily through hypogonadism; it can also include direct toxic effects on bone and developmental maturation.[81,82]

Hypogonadism can be either an intended result of cancer therapy (e.g., in hormone-dependent disease) or an unintended side effect. Early menopause is associated with lower BMD and increased fracture.[82] In patients with BC, osteoporosis at older ages may be accelerated through a number of mechanisms, including premature menopause resulting from chemotherapy, hypo-oestrogenaemia as a result of aromatase inhibition, deliberate ovarian ablation, or medical or surgical castration.[83-86]

Ovarian ablation (either medical or surgical) accelerates bone loss in premenopausal women. Older adults with a history of premenopausal BC may therefore be at an increased risk of osteoporosis than adults of similar age.[85] Even after natural menopause, ovarian ablation with oophorectomy may be associated with increased numbers of skeletal events.[83]

Tamoxifen is associated with a modest beneficial effect on BMD in postmenopausal women and a small decrease in BMD in premenopausal women.[84] Aromatase inhibitors (AIs) have shown enhanced efficacy compared to tamoxifen and are increasingly being used in the adjuvant treatment of postmenopausal women with hormone-sensitive BC. The common finding in studies comparing AIs with tamoxifen is an increased risk of bone loss and of fractures in women taking AIs. Amongst the few trials that have compared AIs with placebo, there is at least a trend toward increased fracture rates in patients taking AIs than in age-matched controls.[83]

Chemotherapy may cause direct toxicity to the ovarian follicle and result in hypogonadism, in addition to its potential direct toxic effects on bone cells.[83,84]

Although cancer treatment-induced bone loss is the major cause of osteoporosis in cancer patients and survivors, other causes should be excluded. These include vitamin D deficiency, hyperthyroidism, hyperparathy-

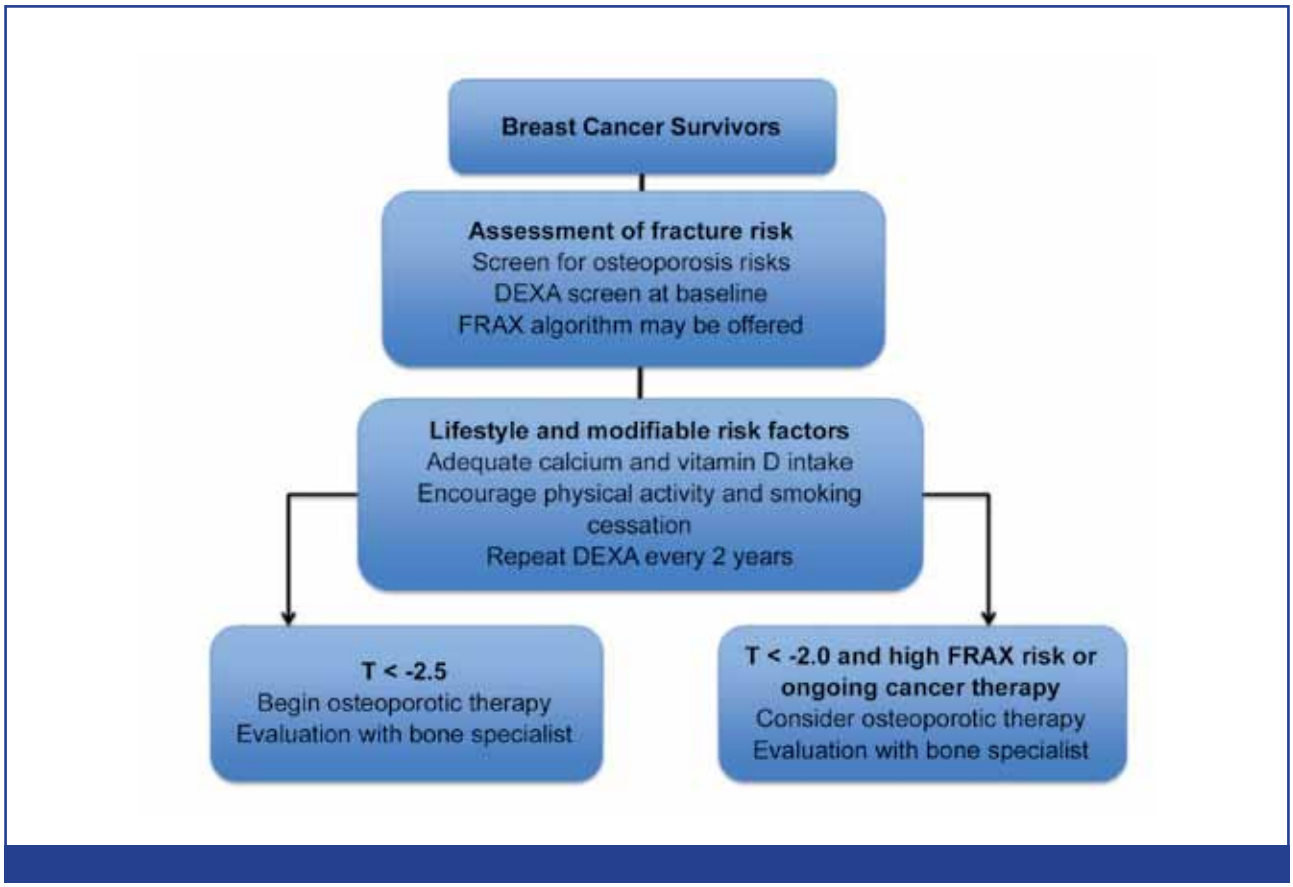

Figure 1. Summary of the task force recommendations on the prevention and treatment of cancer treatment-induced bone loss

roidism (primary or secondary), and idiopathic hypercalciuria. Secondary causes of bone loss are frequently seen in BC patients, with vitamin D deficiency being the most frequent one.[87,88]

Bone assessment

The current gold standard to assess bone loss is dual energy X-ray absorptiometry (DEXA).[83,89] BMD should be measured at the hip and spine, being the fracture sites with the greatest morbidity and mortality rates.[83,89] To increase the predictive ability of DEXA and incorporate additional clinical factors to predict fracture risk, particularly for women with non-osteoporotic DEXA T-scores, the World Health Organization (WHO) developed a fracture risk index (FRAX) tool, which estimates the 10-year risk of any major fracture and hip fracture based on age, race, nationality, body mass index, medications, medical history, family history, smoking and alcohol consumption, and BMD.[83] Only a few of these factors need to be entered for an accurate assessment. It should be noted that FRAX was not developed for cancer treatment-related bone loss and hence requires further validation in cancer patients.

Other approaches have been investigated to overcome some of the limitations of DEXA.[89] Quantitative computed tomography (QCT) measures both volumetric bone density and architecture. However, WHO osteoporosis criteria cannot be applied to QCT derived data, and there is insufficient evidence at present about the superiority of QCT over DEXA. In quantitative ultrasound (QUS), bone integrity is measured by broadband attenuation of a sonographic pulse that is transmitted across the heel and the speed of sound. However, the poor reliability of everyday QUS and the inability to apply T-scores using a peripheral site prohibit its use as a tool for monitoring therapeutic or time-related bone changes. QUS may serve as a screening tool with recommendation to perform DEXA-BMD when indicated. Using biomarkers to predict fracture risk or monitor results of therapeutic interventions in BCS has not been established.

Current clinical guidelines for the prevention and treatment of cancer treatment-induced bone loss[89,90]

Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network

(NCCN) have issued guidelines to identify, monitor, and manage bone health in BCS.

ASCO guidelines recommend BMD screening for all women over the age of 65, and in women aged 60 to 64 with any of the following: family history of fractures, body weight <70 kg, prior non-traumatic fractures, use of an AI, and premature ovarian failure.[89,90] BMD evaluation by DEXA should be repeated annually unless the patient is considered low-risk. Of note, reimbursement criteria in Belgium allow DEXA evaluation every other year. All women should have adequate calcium (1200 mg/d) and vitamin D (400-800 IU/d) intake, engage in physical activity (e.g., weight bearing exercise) and stop smoking. Pharmacological treatment is indicated when BMD T-score is ≤ -2.5 or if the patient has a prior fragility fracture.

NCCN guidelines are comparable to ASCO guidelines. A recent update recommends that a baseline BMD assessment and FRAX algorithm be performed in any patient on cancer therapies that include the following: premature ovarian failure, adjuvant hormone therapy that reduces oestrogen or interferes with oestrogen action, and glucocorticoids. BMD evaluation by DEXA should be repeated every 2 years in patients receiving treatments known to cause bone loss; annual evaluation is recommended if accelerated bone loss is suspected or therapeutic intervention applied. With regard to pharmacological treatment, NCCN strongly suggests that pharmacological treatment be considered at a T-score < -2.0, particularly if additional risk factors are present.

Patients with T-scores > -2 should be managed according to BMD loss during years 1 to 2. In case of unsatisfactory compliance or decreasing BMD on an oral anti-resorptive agent, switching to an IV formulation should be considered.

The BSMO taks force recommendations are summarized in *Figure 1*.

Cognitive dysfunction in women with breast cancer

Most patients with early BC are offered adjuvant chemotherapy, which is followed by endocrine therapy for patients with hormone-sensitive tumours. Cancer treatment has been implicated in both short- and long-term effects on cognitive function in BCS. Post-treatment cognitive changes frequently include problems of attention, concentration, working memory, and executive function.[91] Cognitive impairment can be problematic for BCS, with many asserting that it is their most troublesome post-treatment symptom.[92] Survivors report diminished quality of life and daily functioning as a result of "chemobrain".

There is an increasing body of evidence about the effects of BC therapy on cognitive function. In cross-sectional studies of BCS, 17% to 75% were found to have deficits in attention, concentration, working memory, and executive function from 6 months to 20 years after exposure to chemotherapy.[91] However the lack of pre-chemotherapy assessments limits the conclusions that can be drawn from these studies. Hence longitudinal studies were set up that included pre-treatment neuropsychological assessments (*Table 5*, page 151).[89,93-96]

An exhaustive list of longitudinal studies of cognitive effects of adjuvant therapy in women with BC can be found in the review by *Ahles et al*.[91] Longitudinal studies are consistent with the cross-sectional studies and suggest that a number of patients experience post-treatment cognitive problems, and its incidence has been estimated at 15% to 25%.[91] However, the longitudinal studies have shown a less consistent pattern of post-treatment cognitive decline and challenge basic assumptions made in the field.[91] Several studies found that up to 30% of patients with BC had a lower than expected cognitive performance based on age and education at the pre-treatment assessment, and this did not seem to be related to psychological factors, fatigue, or surgical factors.[91] Hypotheses for this phenomenon include the biology of cancer (e.g., inflammatory response triggering neurotoxic cytokines) and/or common risk factors for the development of BC and cognitive changes (e.g., poor DNA repair mechanisms). Other mechanisms for chemotherapy-induced cognitive changes include direct neurotoxic effects, DNA damage, oestrogen or testosterone reduction, as well as genetic polymorphisms that may render individuals more susceptible to these effects.[104]

Evidence to date suggests that either the combination of chemotherapy and endocrine therapy or endocrine therapy alone may cause cognitive dysfunction.[91]

Cognitive function assessment

The gold standard for assessment of cognitive function is objective neuropsychological (NP) testing.[105,106] Performance on neuropsychological tests is compared with a reference group to determine the presence of cognitive compromise. One recommended battery for use with BC patients includes measures of premorbid intellectual ability, working memory, learning and memory, information-processing speed and efficiency, and spatial and retrieval skills. Self-report measures are

Table 5. Cross-sectional and longitudinal studies of cognitive effects of adjuvant therapy in women with BC

Author	Methodology	Results
Tchen, 2003.[95]	**Subjects:** 100 matched pairs (adjuvant chemotherapy and healthy controls) **Tests:** high-sensitivity cognitive screen (memory, language, attention/concentration, visual motor, spatial, psychomotor speed, and executive functions); quality of life	Patients (*vs* controls) had: - higher incidence of moderate or severe cognitive impairment (16% *vs* 4%) - more fatigue and menopausal symptoms, and worse quality of life, especially in physical and functional domains - there was a strong correlation between fatigue, menopausal symptoms, and quality of life, but none significantly associated with the presence of cognitive dysfunction
Mar Fan, 2005[96]	1- and 2-year follow-up of the above trial	Moderate to severe cognitive dysfunction decreased from 16% to 4% over 2-year follow-up; no difference in cognition between ER-positive patients who started hormonal therapy (mainly tamoxifen after chemotherapy) and ER-negative patients who did not
Arndt, 2005[97]	**Subjects:** 314 BC patients at three time points: T0 (shortly after diagnosis), T1 (1 year after diagnosis), T2 (three years after diagnosis) **Tests:** EORTC quality of life questionnaire C30 and BC specific module BR-23	- overall quality of life and physical functioning comparable to general population 1 year after diagnosis - deficits in emotional, social, role and cognitive functioning still present, predominantly in younger women, and persisting over time
Hurria, 2006[8]	Older patients with BC – patients' perspective	Patient perception of decline in cognitive function (pre-chemotherapy *vs* 6 months after chemotherapy) in about 50%; most pronounced in patients who perceived pre-existing problems
Hurria, 2006[99,100]	**Subjects:** 28 older BC patients, adjuvant chemotherapy **Tests:** neuropsychological testing and comprehensive geriatric assessment (CGA) before and after 6 months	- Number of test scores 2 standard deviations below normative data calculated at each time point: 50% patients had no change, 39% worsened, 11% improved - exploratory analyses of longitudinal CGA: no changes in functional status, comorbidity, depression
Wefel, 2010[101]	**Subjects:** 42 BC patients T1-3, N0-1, M0 receiving 5-fluorouracil, doxorubicin, and cyclophosphamide with or without paclitaxel **Tests:** neuropsychological evaluation including measures of cognition, mood, and quality of life; assessment before chemotherapy, during and shortly after chemotherapy, and 1 year after completion of chemotherapy.	- 9 of 42 (21%) cognitive dysfunction before chemotherapy - 24 of 37 (65%) cognitive decline in acute interval - 17 of 28 (61%) cognitive decline after cessation; 12 of 17 (71%) had continuous decline, 5 of 17 (29%) had new delayed cognitive decline - cognitive decline most common in domains of learning and memory, executive function, and processing speed
Ahles, 2010[102]	**Subjects:** BC patients with chemotherapy (n=60), no chemotherapy (n=72), healthy controls (n=45) **Tests:** verbal ability, verbal memory, visual memory, working memory, processing speed, sorting, distractibility, reaction time, self-report measures of depression, anxiety, fatigue, cognitive ability; testing before treatment, at 1, 6, and 18 months after treatment	- significant effects for processing speed and verbal ability - processing speed: lower performance in older patients with lower baseline cognitive reserve exposed to chemotherapy *vs*. patients not exposed to chemotherapy or healthy controls - verbal ability: short-term impact of chemotherapy (failure to improve at 1 month assessment, improvement during last 2 follow-up assessments)
Koppelmans, 2012[103]	**Subjects:** BCS, >20 years after adjuvant CMF chemotherapy	- BCS performed worse than random population controls - pattern of cognitive problems similar to that observed in patients shortly after cessation of chemotherapy

also available for assessment of subjective cognitive complaints, although these do not necessarily correlate with objective cognitive impairment. It is possible that women may be sensitive to subtle changes in cognitive function that are not picked up by objective tests or that subjective measures are more strongly influenced by other behavioural problems, such as depression or fatigue.

Data from imaging studies support the hypothesis that chemotherapy affects brain structure and function.[91] Several cross-sectional, post-treatment studies using MRI have documented reductions in grey matter, primarily in frontal structures and the hippocampus, and in white matter integrity in cancer survivors treated with chemotherapy. Longitudinal studies have reported similar results. Cross-sectional studies of cancer survivors using functional imaging techniques, including functional MRI (fMRI) and functional positron emission tomography (fPET) have demonstrated areas of decreased activation during the performance of a cognitive task in survivors who had had chemotherapy versus controls, similar to the differences described in the structural imaging studies. In a review of published studies, *Vardy et al.* concluded that there was a lack of consistency in both the NP batteries used to assess the cognitive function of cancer patients and in the statistical methods applied.[105] They strongly recommend using summary scores and control groups. Adjustment for practice effect should be made in longitudinal studies. A balance is needed between comprehensive batteries and briefer tests, which still need to be sensitive to mild impairment. guidelines for research are clearly needed.[107]

From a basic research point of view, it is interesting to view cognitive change within the context of factors that influence the trajectory of normal aging.[91] Research into specific pathways associated with aging suggests that biologic processes underlying cancer, the impact of cancer treatments, aging, neuro-degeneration, and cognitive decline are linked. In addition to examining specific pathways, the concept of systems theories provides an interesting framework for hypotheses generation and research.[91]

The reliability theory of aging proposes that complex biologic systems have developed a high level of redundancy to support survival. One implication of this theory is that vulnerability to post-treatment cognitive change does not necessarily depend on a given treatment affecting a specific biologic pathway; rather, different patterns of failure rate (redundancy loss) across various biologic systems may confer more or less vulnerability to specific treatments for a given individual, and this vulnerability may be influenced by pre-treatment patterns of system failure. Another implication of this theory is that it challenges the assumption that long-term cognitive problems result from the lack of recovery from the acute effects of treatment, but remain stable thereafter. Within the framework of aging models, two hypotheses can be identified: one, that age-associated declines parallel those of (older) adults with no cancer history (phase shift), or two, that adults who had cancer follow a steeper slope of decline (accelerated aging). This highlights the need for studies examining the impact of cancer and cancer treatments on the trajectory of age-associated cognitive change, particularly in older cancer survivors.

Interventions for chemotherapy-related cognitive impairment in BC patients have not yet been developed and evaluated.[91] However, results from a pilot study suggest that a cognitive-behavioural approach may be effective. *Ferguson et al.* conducted a single-arm cognitive behavourial therapy (CBT) intervention with BCS who reported problems with memory and attention several years after chemotherapy.[108] Participants were provided with information about chemotherapy-related cognitive problems, learned how to identify at-risk situations where cognitive problems might occur, and were trained in the use of compensatory strategies to help manage these situations (e.g., schedule making, external cueing). There were significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups. These findings require replication in a randomised controlled trial, but they suggest that this type of programme may be feasible and effective for BCS with persistent cognitive impairment.

Other potential treatment approaches include methylphenidate, which has been used to improve cognitive function in patients with advanced cancer.[109] There are no proven interventions for preventing or treating chemotherapy-related cognitive impairment. Small randomised studies of erythropoietin, modafinil, and other agents have failed to show convincing improvement in cognitive function.[54]

Recommendations

All patients shoul be informed that neuro-psychology services are available, and that these services may help them to deal with their attention and memory problems. The following assessment may be performed, by

a trained person, before and after chemotherapy:

1. Short neuro-psychology hystory
2. Montreal Cognitive Assessment (MOCA).[110]
3. Hospital Anxiety and Depression Scale (HADS) and 3 specific items focusing on subjective cognition for memory, speed and attention.[111]
4. If MOCA detects any deficit at any assessment, a more extensive evaluation in the affected function is recommended

Table 6. Early BC clinical trials with reported taxane-induced neuropathy

Study	Patients (n)	Regimen	Neurotoxicity G1-G2	Neurotoxicity G3-G4
MDACC (2002)[113]	259 265	FAC x 8 q3-4w P 250 x 4 q3w -- FAC x 4 q3w	NR NR	0.005% 5%
CALGB 9344 (2003)[114]	1580 1590	AC x 4 q3w AC x 4 4 q3w -- P x 4 q3w	NR 15%	NR 3%
Int C 9741 (2003)[115]	484 493 501 495	A x 4 q3w -- P x 4 q3w--C x 4 q3w A x 4 q2w -- P x 4 q2w--C x 4 q2w AC x 4 q3w -- P x 4 q3w AC x 4 q2w -- P x 4 q2w	NR	4% 4% 5% 4%
NSABP B28 (2005)[116]	1529 1531	ACx 4 q3w AC x4 q3w -- P x 4 q3w	NR	NR 15%
BCIRG 001 (2005)[117]	746 745	FAC x 6 q3w TAC x 6 q3w	10.2% 25.5%	0% 0%
Anglo-Celtic (2005)[118]	180 183	AC x 6 q3w AD x 6 q3w	NR NR	0% 0%
HeCOG 10/97 (2005)[119]	298 297	E x 4 q3w -- CMF x4 q2w E x 3 q2w -- P x 3 q2w -- CMF x3 q4w	NR NR	0% 6%
E 1999 (2008)[120]	1253 1231 1236 1230	AC x 4 q3w -- P x 4 q3w AC x 4 q3w -- P x 12q1w AC x 4 q3w -- D x 4 q3w AC x 4 -- D x12 q1w	20% 27% 16% 16%	5% 8% 4% 6%
BIG 02-98 (2008) [121]	481 487 960 959	A x 4 q3w -- CMF x 3 q3w AC x 4 q3w -- CMF x 3 q3w A x 3 q3w -- D x 3 q3w -- CMF x 3 q3w AD x 4 q3w -- CMF x3 q3w	frequent	rare (< 5%)
GEICAM 9906 (2008)[122]	632 614	FEC x 6 q3w FEC x 4 q3w -- P 100 x 8 q1w	NR 22.2%	NR 3.7%
GEICAM (2010)[123]	521 539	FAC x 6 q3w TAC x 6 q3w	7.5% 19.3%	0.2% 0.2%
NCIC MA 21 (2010)[124]	701 702 701	CEF x 6 q 4w AC x 4 q3w -- P 175 x 4 q3w EC x 6 q2w -- P x4 q3w	NR NR NR	0.3% 5.5% 6%

A: doxorubicin; AC: doxorubicin, cyclophosphamide; AD: doxorubicin, docetaxel; C: cyclophosphamide; CEF: cyclophosphamide, epirubicin, fluorouracil; CMF: cyclophosphamide, metotrexate, fluorouracil; D: docetaxel; DC: docetaxel, cyclophosphamide; E: epirubicin; EC: epirubicin, cyclophosphamide; FEC: fluorouracil, epirubicin, cyclophosphamide; P: paclitaxel; TAC: docetaxel, doxirrubicin, cyclophosphamide.

Table 7. Total Neuropathy Score (TNS)

Parameter	SCORE				
	0	**1**	**2**	**3**	**4**
Sensory symptoms	None	Symptoms limited to finger and toes	Symptoms extend to wrist or ankle	Symptoms extend to elbow or knee	Symptoms above elbow or knee or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in finger or toes	Reduced up to wrist or elbow	Reduced to elbow or knew	Reduced above elbow or knee
Vibration sensibility	Normal	Reduced in finger or toes	Reduced up to wrist or elbow	Reduced to elbow or knee	Reduced above elbow or knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflex absent
Vibration sensation (QST vibration)	Normal to 125% of ULN	126% - 150% of ULN	151%-200% of ULN	201%-300% of ULN	> 300% of ULN
Sural amplitude	Normal reduced to < 5% of LLN	76%-95% of LLN	51%-75% of LNN	26%-50% of LLN	0% -25% of LNN
Peroneal amplitude	Normal reduced to < 5% of LLN	76%-95% of LLN	51%-75% of LNN	26%-50% of LLN	0% -25% of LNN

LLN: lower limit of normal; ULN: upper limit of normal; QST: quantitative sensory te

Neurotoxicity with adjuvant therapies

Taxane-induced peripheral neuropathy is one of the major and most common non-haematological side effects in early BC. This affects not only quality of life, but also treatment outcomes due to dose reduction and treatment discontinuation.[112] The severity of taxane-induced peripheral neuropathy is generally mild to moderate during chemotherapy treatment; approximately 15% to 27% of patients included early BC trials with taxanes developed Grade 1-2 peripheral neuropathy and 0% to 8% developed Grade 3-4 (*Table 6*).[113-124] Commonly, mild neuropathy usually improves or resolves after chemotherapy discontinuation, whereas severe neuropathy persists longer.[125] However, there are few data on the prevalence and severity of long-term taxane-neurotoxicity. Taxane-based chemotherapy predominantly induces distal, symmetric axonal sensory neuropathy characterised by paraesthesia, numbness, tingling, pain in the hands and feet, and loss of tendon reflex.[126,127] The thick, myelinated nerve sensor fibres of vibration and perception are the fibres most commonly affected, while motor or autonomous fibres are rarely affected.[128,129] Because taxane-induced neuropathy is dose-dependent, cumulative dose and dose received per cycle are the most relevant risk factors for its development.[130] Nevertheless, pre-existing neuropathies such as those associated with diabetes mellitus (DM), alcohol consumption, malnutrition, monoclonal gammopathies, and age play an important role in prompting taxane neuropathy.[128] The diagnosis of taxane-induced neuropathy is based on clinical examination and neurophysiological assessment methods that make it possible to classify different types of neuropathy and are helpful for differential diagnosis. Regarding neuropathy classifications and grading scales, many efforts have been made to establish neuropathy grading scales such as the NCI Common Toxicity Criteria (CTC) and the Gynecologic Oncology group (GOG)-neurotoxicity (FACT/GOG-Ntx) criteria in clinical

practice.[131,132] However, because of wide inter- and intra-observer variation, these scales lack general acceptance; this could explain the marked variation observed in taxane-induced neuropathy in early BC clinical trials (*Table 6, page 153*). Cavaletti et al. have therefore proposed the Total Neuropathy Score (TNS), which includes symptoms and electrophysiological measurements, enables accurate classification, and increases reproducibility amongst trials (*Table 7, page 154*).[133]

In addition, chemopreventive agents including vitamin E, glutathione, amifostine, glutamine, calcium, and magnesium have been tested to decrease neuropathy during chemotherapy treatment.[134-136] Despite some positive results, there are insufficient data to conclude that any of them should be administered as standard therapy to prevent taxane-induced neuropathy. Furthermore, one of the most challenging aspects of this toxicity is that there is no reliable method to determine patients at a higher risk of developing it. Therefore, great effort in pharmacogenomics is focused on determining genetic factors that may be involved. ABCB1 and GSTM1 are some of the genes that have been shown to play a role.[137] Nevertheless, methodological and validation issues remain to be solved before techniques derived from genetic factors can be implemented in daily practice.

It is essential however to use accurate neuropathy scales to address the real prevalence and severity of acute and long-term neurotoxicity. Furthermore, it is also critical to invest in translational research to identify patients with a higher risk of neurotoxicity and to facilitate decision making for clinicians and patients prior to initiating taxane-based chemotherapy.

Summary of recommendations regarding neuropathy

1. Neurotoxicity is common with taxane-based chemotherapy
2. It usually improves or recovers when taxanes are stopped
3. There is a lack of long-term data on prevalence and severity of taxane-induced neuropathy
4. Diagnosis is based on clinical examination and neurophysiological assessment methods
5. There are no standard chemopreventive agents, though some agents can be used to reduce the severity of neuropathy.

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