Abstract

Breast cancer is the most frequently diagnosed neoplasm and the first cause of death in women, especially under the age of 40. Hereditary and genetic syndromes are more prevalent among young breast cancer patients and require genetic counseling. Young women also exhibit larger tumors, with more frequent nodal involvement and more aggressive features (triple negative, high grade and proliferation rate) than menopausal women. Fertility preservation and pregnancy-associated cancer are specific issues in this age group and need to be addressed accordingly.

Keywords: Breast Cancer in Young Women; Breast Cancer and Pregnancy; Fertility Preservation; Hereditary Cancer Syndromes

Abbreviations

BC: Breast Cancer; BCY: Breast Cancer in Young Women; ALNI: Axillary Lymph Node Involvement; TN: Triple Negative Tumour; LFS: Li-Fraumeni Syndrome; MRI: Magnetic Resonance Imaging

Introduction

Breast cancer is the leading neoplasm among women all ages, including women under 35, and remains at the first rank on the cancer-related death burden. Women younger than 50 are not undergoing screening in most European countries, thus cancer diagnosis results from clinical symptoms, and may be difficult and delayed (dense breasts, pregnancy). Young women exhibit larger tumors with more frequent nodal involvement than older women. Recent data suggest aggressive tumor characteristics and a higher relapse rate in [1]. Prognosis is therefore less favourable and mortality higher than the general breast cancer population. Because of their younger age, these patients need special care, such as fertility-sparing treatment options. Family history and familial cancer syndromes are more prevalent in very early onset breast cancer; thus genetic predisposition identification is crucial, since it may influence treatment, follow-up and surveillance of other family members.

Materials and Methods

A literature review was performed using the key words “breast cancer in young women”, “breast cancer in pregnancy”, “fertility preservation of breast cancer” on PubMed database. A selection was made for the most recent publications.

Results and Discussion

Epidemiology

ESMO Consensus conference on breast cancer in young women (BCY3) [2] sets a cut-off at 40 years old (yo) at the time of the diagnosis. Still, published data is not unanimous regarding the cut-off age, some series concern women less than 40, others 50 and some segregate women into menopausal or premenopausal. In clinical practice, regarding tumoral behaviour and therapeutic modalities derived
from it, it seems reasonable to distinguish BC occurring in young women (< 40 yo), from BC occurring in premenopausal women (40 to about 50 yo) and BC occurring in menopause women (usually after 50 yo).

Breast cancer is the first neoplasm among women, and remains the first in women under 35, accounting for the highest number of cancer-related deaths [3]. It affects one woman in 300 before 40 yo according to Globocan in 2008 and represents about 7% of all breast cancer cases [4].

Several countries [5], including Switzerland [6,7], report a trend towards a raise in the incidence of BC in young women. More recent data from the American Cancer Society in 2018, suggest that BC would affect one woman in 220 before 40 yo.

Clinical presentation

Palpation of a breast lump is the usual clinical onset. Cases have been reported where the diagnosis is made during infertility work-up [8]. A diagnostic delay has specially been reported during pregnancy or when patients complain of other symptoms than lump [9,10]. Thus, tumoral size is significantly larger than those detected with screening [11,12]. Axillary nodal involvement is also present in half of the cases. The older the patients are, the smaller tumours are and the more they get localized to the breast parenchyma only.

At onset, BC is localized to the breast in 45% of cases, axillary nodal involvement in 50% of cases and metastatic in 5%. In comparison, ALNI is present in less than 30% of the screening population.

Risk factors

Genetic predisposition and family history

Familial and genetic predispositions are more prevalent among BCY.

Family history is associated with a relative risk of 3.22 under 35 yo and seems to be the only factor associated with TN [1,13,14].

BRCA1 and BRCA2 gene mutations account for 10% of BCY, whereas they represent only 3% in the general BC population [15]. It is highly associated to TN. Other high and intermediate penetrance mutations, responsible for hereditary cancer syndromes were identified and are tested after genetic counseling. They include Li-Fraumeni syndrome (p53 mutation), Cowden (PTEN) and Peutz-Jeghers (SKT11). CHECK2 mutation, for instance, exposes to a doubled risk of BC, but not early-onset as for LFS, where half of the affected women will declare BC before 30yo. Indications for oncogenetic counseling are described under the paragraph 6.12 and the spectrum of cancer syndromes can be found in the publication of Zeichner, et al [49]. When a mutation is identified, planned treatment could be modified, especially contralateral prophylactic surgery or screening through MRI. In the case of LFS, radiation therapy is contraindicated due to the risk of second tumours.

Other risk factors

Traditional BC risk factors such age at menarche, parity and breast-feeding seem less contributive in BCY.

Other risk factors were under research, notably the effect of oestroprogestative pill presenting a slightly additional risk, which lowers after cessation [16]. Parity is a well-recognized protective factor in menopause, but there seems to be a transient augmentation in BC risk up to 15 years post-partum [17].

The effect of the weight is more and more clear: obesity is a risk and a prognostic factor after menopause as well as before [18].

A history of thoracic radiotherapy, notably in childhood and specially for Hodgkin lymphoma, sets the patient at a 10% risk of developing BC before 45 yo [1].

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Imaging

Ultrasound remains the key tool due to high breast density in young women. MRI might be difficult to analyse, its indications are lobular histology and suspicion of multifocality, it might also be used as screening for BRCA mutated patients. American college of radiologists recommends starting screening at 40 yo for women with a high-risk family history [19]. Personalized screening is under investigation in several countries and might represent an option for early detection in the future.

Differential diagnosis

Benign pathologies like cysts or fibro-adenomas are more frequent than BC and imaging work-up helps orient the diagnosis and core biopsy rule out any doubt. When regarding differential diagnosis, there are inflammatory conditions, (such as diabetic mastopathy and chronic idiopathic granulomatosis), affecting women between 20 and 40 yo with immune background, and chronic infections (actinomycosis, tuberculosis) which mimic neoplasm, especially inflammatory carcinoma. Among primary breast tumours are primary breast sarcoma, affecting young women without history of previous irradiation, in opposition to radio-induced sarcoma. Although rare, these are highly aggressive with a different tumoral spread pattern than epithelial BC.

Tumour characteristics

Apart from larger tumour size, other aggressive factors are interfering. Several studies [1-5] have shown that aggressive biological types like TN and HER2 positive were overrepresented in younger women compared to older (TN 18% vs 10%, HER2+ (including luminal B) 33% vs 16%).

Young patients exhibit higher grade (70%) and proliferative tumours (Mib1 > 15: 70%) than the general BC population [20]. Surprisingly, hormono-sensitive tumours, usually of good prognosis, are graved with a worse prognosis in young women, associated a significative specific death rate for luminal A (HR, 2.1; 95% CI, 1.4 à 3.2) and luminal B (HR 1.4; 95% CI, 1.1 to 1.9) [21].

Finally, inflammatory carcinoma, known to be particularly aggressive, accounts for 2% of all BC [22], 6% in women less than 45yo.

Treatment

Treatment is guided by tumour characteristics as for older BC patients. Because of tumoral size, nodal involvement and overrepresentation of aggressive types, young women undergo neoadjuvant chemotherapy more often than the usual BC population [10]. When breast conserving surgery is performed, radiotherapy frequently comprises a boost on tumour bed.

For high risk patients (< 35 yo, grade 3, > 4 involved lymph nodes, not menopaused after chemotherapy), hormonotherapy consists of an aromatase inhibitor for 5 to 10 years, with a GnRH agonist (or oophorectomy). SOFT (tamoxifen/tamoxifen + ovarian suppression/exemestane and ovarian suppression) and TEXT (ovarian suppression + tamoxifen or exemestane) studies [23,24] reveal a longer disease-free survival with the association exemestane and ovarian suppression. Hormonotherapy with tamoxifen is only for low-risk patients.

Due to teratogenic effects, non-hormonal contraception has to be proposed to all women in reproductive age. Hormonal contraception is contraindicated independently from biologic type.

Hormonotherapy is grieved with undesirable effects (menopausal symptoms, osteoporosis) and non-adherence to treatment is as high as 30 - 40% of patients [25].

Regarding premature menopause and osteoporosis risk, GnRH agonists lower the risk of premature ovarian insufficiency from 30 to 14% [26], addition of bisphosphonates is recommended in case of occurrence of osteoporosis [2]. Menopausal symptoms can be managed with a dose reduction or change in the molecule, as well as cimifemine or antidepressant introduction [27].
Overview of Diagnosis and Treatment of Breast Cancer in Young Women

Prognosis and relapse

5 years survival rate is 84% for BCY compared to 90% for the whole BC population [28,29]. This is due to BCY aggressive characteristics and to a lesser adherence to adjuvant hormonotherapy [30].

A higher relapse rate was demonstrated in young women after breast conserving surgery (15% in women less than 35 yo versus 3% in women aged 45 to 49 yo), nevertheless without impact on survival [31]. The risk of contralateral tumour development reaches 0.5% per year [32].

Fertility preservation

Up to a quarter of patients will question therapeutic propositions because of concerns about fertility [33]. Even if it does not directly involve reproductive organs, BC is the second leading cause, after cervical cancer, of non-realized pregnancy project [34].

Due to potential gonadotoxic effect of some chemotherapy agents, patients in reproductive age with an open familial planning should be referred to a fertility specialist before treatment initiation.

Fertility alteration depends from age at diagnosis, initial ovarian reserve and chemotherapy type, molecules being classified upon their gonadotoxicity. Agonists allow ovarian blockage and thus to minimize follicular alteration, with proved results in terms of restoration of ovarian functioning and pregnancies obtained but is not considered per se a fertility preservation technique. Three techniques are available depending on age and patient’s relational status: ovarian cortex uptake, immatures or matures oocytes uptake and embryo cryo-conservation [35]. Embryo cryo-conservation implies having a partner. Ovarian cortex uptake is suitable before menarche. The choice of the technique depends on timing available and multidisciplinary discussion with the fertility specialist.

Adjuvant hormonotherapy, usually prescribed for 5 years, is a contra-indication to pregnancy. This fact has to be taken in account in patients diagnosed in mid-thirties who will wish to get pregnant after adjuvant treatment, bringing them around forty when follicular reserve is lowering.

Moreover, recent studies [36,37] reveal a further significant shrinking in AMH levels in BRCA1 carriers, emphasizing the importance of identifying the women in order to offer them the best chance of eventual pregnancy.

Breast cancer and pregnancy

BC is the first cancer complicating a pregnancy, followed by cervical cancer and melanoma.

Pregnancy-associated breast cancer is defined as occurring during pregnancy and the year after or during breast-feeding. It concerns up to 14% of BCY cases depending on the age group studied [38]. Every breast lump should be radiologically assessed: ultrasound is the first intention tool, mammography can be performed with shielding of the foetus and MRI is preferred without gadolinium [39]. PET scanner is contraindicated.

Up to 10% of BCY are diagnosed in the course of pregnancy. This is due to the rising incidence of BC on one hand and to older maternal age on the other hand. Parity has a long term protective effect, but there seems to be a transient rise in risk for about ten years post-partum [38]: in cause are the accelerated glandular modifications, associated with an escape from the immune system through HLA G modulation, a physiologic phenomenon of immunotolerance during pregnancy. Patients with BC occurring up to 10 years postpartum have a significantly higher risk of metastatic spread than do nulliparas, even after adjustment for age and biological characteristics [40].

Management of BC during pregnancy has to stay as close as possible to the one that would be proposed if the patient was not pregnant [41]. Pregnancy cessation does not modify prognosis beyond the first trimester and is therefore not preconised for medical reasons. Sentinel lymph node biopsy with radio-isotope can be performed, although blue dye should not be used due increased risk of anaphylactic reaction. In the first trimester, chemotherapy is contraindicated due to embryogenesis, but can be used in the second and third trimester. Ideally, chemotherapy is stopped 2 to 3 weeks before delivery and labour should not be induced before 37 weeks’ gestation, except for...
obstetrical indications. Radiotherapy and immunotherapy are contraindicated during the pregnancy and should be planned after delivery [42]. Neonatal implications are caused mainly by iatrogenic prematurity [43]. Management of BC diagnosed in the post-partum period are no different than the standard BC treatment guidelines.

**Contraception and pregnancy after breast cancer**

Contraception recommendations are the same as during treatment, which means options are copper intra-uterine device, condoms or tubal ligation.

Less than 10% of patients with a previous BC initiate a pregnancy after completion of the treatments [34]. There is no contra-indication to pregnancy even if the treated BC was hormone-sensitive [44]. Published data [45,46] shows no decrease in disease-free survival, under the condition of the “healthy mother” effect. Conception seems safe 2 to 3 years after the end of the treatments, since relapse rate is the highest within the first 2 years. Breast feeding is not contraindicated.

This timing is problematic for women around 35 - 40 yo, by whom the ovarian reserve will have declined by the end of the treatments. The ongoing prospective POSITIVE trial of the International Breast Cancer Study Group allows enrolled women a break in hormonotherapy (after 2 years of treatment) in order to initiate a pregnancy. After breast-feeding, hormonotherapy is re-introduced to complete 5 years in total. A period of 3 months is warranted before trying to conceive.

**Genetic counseling**

All women under 40 yo should be addressed for genetic counseling, other indications include family or personal history of ovarian cancer, history of another primary BC, TN BC under 60 yo, family history of more two breast cancers and male breast cancer. Detailed NCCN guidelines for genetic counseling and testing are available in their publication [48]. Several tests exist, but mostly screen 10 high (BRCA 1/2, p53, PTEN) and moderate to high penetrance genes. The indication to this testing is determined by the onco-genetician based on clinical case and family history.

Management of BRCA 1/2 carriers includes annual breast surveillance with MRI starting at 25 yo and gynecological examination twice a year from 30 yo or 5 years earlier than the first tumour in the family. Bilateral mastectomy reduces relapse rate by up to 90%, although the effect on overall survival is less clear. Salpingo-oophorectomy is indicated from 35 resp. 40 yo (BRCA 1 resp 2) or upon completion of family planning. For men, surveillance consists of breast auto palpation from 35 yo and prostate screening from 45 ans. In case of BRCA 2 mutation and family history of pancreatic cancer, a specific surveillance can be discussed. The testing can be proposed to relatives of BRCA carriers, if they wish to know their status.

For LFS patients, a screening of the others tumours in the spectrum is performed through yearly total body MRI. Patients with p53 and ATM mutations have a higher risk or developing secondary tumours and radiotherapy is, therefore, contraindicated. The principle of sparing young high-risk women and those with a history of chest wall radiation is important given the risks of repeated exposure to ionizing sources cumulated throughout their life.

Follow-up and screening of other mutations carriers is generally performed through yearly breast MRI and the indication of screening of other target organs will be set by the onco-genetician.

**Psychosocial issues**

Psychosocial implications of a cancer diagnosis in a young woman are beyond the scope of this overview. Nevertheless, half the patients under hormonotherapy present depressive symptoms and a high proportion of young women do not regain their workplace after treatment. Children day-care, work, sexuality and body image are other every day struggles that require the need to offer a support network to these young women.
Overview of Diagnosis and Treatment of Breast Cancer in Young Women

Conclusion

BCY is not rare and is the main cause of cancer mortality under 40 yo. Young women have larger tumours, more often a nodal involvement and aggressive patterns and biologies. Relapses are more frequent, so that age by itself appears as an independent prognostic factor.

Being in the reproductive years, the question of fertility preservation needs to be addressed with patients who have not completed their family planning. Cancer during pregnancy implies special considerations. A higher proportion of genetic predispositions implies referral for counseling in order to optimize treatment, follow-up and secondary prevention.

Thus, BCY differs from menopausal BC from its risk factors, its presentation and the tumoral behaviour. It therefore deserves a specific management, not to mention the economical and psychosocial issues related in women of working age and with families to care about.

Conflict of Interest

The authors declare no conflict of interest.

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Bibliography

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