



Review

Is it time to address survivorship in advanced breast cancer? A review article



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ABSTRACT

The outcome of advanced breast cancer has significantly improved over recent decades. As a consequence, the complex needs of patients living with the disease and their care-givers should be addressed not only in terms of supportive and palliative care but also of “survivorship” requirements. The multidisciplinary approach to advanced breast cancer should encompass – early in the history of the disease – not only physical but also functional, social, psychological and spiritual domains. It is important to clearly define the disease context with patients and families (“chronic” preferred to “incurable”), addressing the concept of uncertainty, and tailoring the treatment strategy according to both disease status and individual priorities. Specific psychosocial needs of young and elderly women and male patients – i.e. social security, job flexibility, rehabilitation (including sexuality), home and child care – should be recognized and supported. This review will address the key questions associated with survivorship in this disease context, recognizing the dearth of specific data and the urgent need for targeted clinical research and tailored interventions.

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1. Introduction

In the last decades, the growing biological knowledge and the availability of effective new drugs have significantly improved the survival of patients with advanced breast cancer (ABC). As a consequence, patients, families, healthcare providers and society as a whole have to face new challenges. Some of the emerging priorities include quality of life (QoL) of both patients and care-givers, job and insurance issues, and costs of treatments at the individual and social level.

The aim of this review is to highlight the clinical, social, psychological, and relational problems associated with the prolonged survival of ABC patients.

2. Who is a cancer survivor?

“An individual is considered a cancer survivor from the time of diagnosis through the balance of his/her life. Family members,

friends and care-givers are also impacted by survivorship and are therefore included in this definition” [1].

Thirty years ago we faced the psychosocial consequences of patients cured of cancer. Today, the increased survival of some ABC patients raises new perspectives requiring a more comprehensive formulation of survivorship. In 2012 the Multinational Association of Supportive Care in Cancer (MASCC) included survivorship as an integral component of supportive care [2], but to date the focus has traditionally been on women living “after” rather than “with” BC [3].

3. How significant is survivorship in ABC?

ABC is the most common cause of cancer death in females worldwide. No systematic and prospective survival data for ABC patients are available, all information being derived from retrospective institutional series.

In patients relapsing after early BC, a retrospective analysis of 834 patients treated between 1974 and 2000 at the MD Anderson Cancer Center [4] showed that early stage of the primary cancer, a long disease-free interval (DFI), estrogen-receptor positivity, and bone versus visceral disease site were independent prognostic factors for longer survival after relapse. In the same series, a

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significant increase in median survival was shown over the years, from 15 months (1974–1979) to 58 months (1995–2000). The survival of 2150 women diagnosed with ABC in British Columbia in the late 1990s improved by approximately 30% compared with women diagnosed in the early to middle 1990s [5].

The timing of ABC onset (de-novo versus recurrence) may also influence outcome. A retrospective analysis of 3524 women treated at the MD Anderson between 1992 and 2007 compared the outcome of 643 patients with de-novo ABC and 2881 patients with recurrent disease. The median overall survival (OS) among patients with de-novo ABC and with relapsed disease was 39.2 and 27.2 months, respectively ($P < 0.0001$). After stratifying for DFI, a DFI < 5 years was associated with a statistically higher risk of death as compared to patients with de-novo ABC. Despite being a retrospective study in the pre-trastuzumab era, these data suggest that de-novo ABC is an entity distinct from disease relapse [6]. An additional French retrospective series of 724 women with de-novo ABC showed a median survival of about 23 months in patients diagnosed in the period 1987–1993 and of about 29 months in patients diagnosed in 1994–2000 [7].

Oligometastatic disease, defined by a limited number and size of metastatic lesions (up to five, not necessarily in the same organ) and brain-only metastases (BO-MBC), represent distinct clinical situations. Data from retrospective studies suggest that a more accurate identification of patients with truly oligometastatic ABC, a long DFI, and a good response to systemic treatments allows for potentially curative intensive therapies [8,9]. Overall, BO-MBC occurs in about 17% of BC patients; this specific patient subset has a more favorable outcome, and long-term survival with multidisciplinary treatment is not uncommon [10].

4. Are psychosocial needs different in ABC patients?

Understanding the needs of ABC patients is crucial for the potential improvement of their QoL. The debate about the impact of psychological support on quality of survival in ABC is still open, and the evidence available on the psychological effects of ABC is limited [11–13].

Clinical research is challenging in this setting of vulnerable patients with different and sometimes limited life expectancy. A substantial proportion of these patients experience psychological morbidity, younger patients being more prone to depressive disorders [14–16]. On the other hand depression may be greatly underdiagnosed in older patients with cancer unless a comprehensive geriatric assessment is routinely done as part of their standard evaluation [17]. Psychological support should balance the 'keep-positive' attitude and the idea of facing death. Addressing rather than avoiding the idea of death/dying may lead to a greater sense of control and empower patients to reorder life's priorities. Uncertainty, lack of control, and poor emotional functioning are frequent; anxiety is also associated with impaired cognitive function [18]. Self image and sexual functioning, not routinely addressed by healthcare providers, challenge self-esteem and relationships [19].

No data on marital/couple breakdown is available in women with ABC. No increase in the risk of divorce was recently demonstrated in a cohort of 134,435 married Finnish women with early BC, with no apparent impact from the type of surgical procedure or the oncological treatments. Individualized psychosocial support is therefore crucial, taking into consideration cultural and social differences [20].

Although suicide may be a recurring thought for some BC patients, studies in BC survivors are rare and retrospective. Suicide risk in cancer patients in California from 1997 to 2006 was 2.3 times that in the general population; ABC was associated with a

significantly higher risk in women [21,22]. In Europe slightly lower risks are reported [23].

In the BC setting an increase in suicide risk, lasting > 25 years after diagnosis, was reported from 16 population-based cancer registries in the US and Scandinavia in patients diagnosed between 1953 and 2001 [24]. In the Basel BC database (1165 patients diagnosed in 1990–2006) a suicidal death was identified in six patients (0.5%), four patients committed suicide during late stages of ABC, two cases were associated with comorbid conditions, and three patients chose physician-assisted suicide (legal in Switzerland). The rate was 2–7 times higher than that reported in epidemiological studies [25]. Systematic screening for suicidal ideation by the healthcare team may identify patients at high risk and facilitate appropriate evaluation and treatment.

The change of supportive needs along the disease journey has been studied in 228 Chinese ABC patients. A longitudinal assessment of four domains (health system/information/patient support, psychological, physical daily living, and sexuality) – conducted at baseline after 6 weeks and after 3, 6 and 12 months – showed stable low levels of all variables in most women. With the exception of sexuality, trajectory patterns were predicted by physical symptoms: women in the high-decline group reported greater physical symptoms [26].

Face-to-face interviews in 220 Chinese women with stage III–IV BC identified health system, information and patient support as the most unmet needs. "Having one member of hospital staff to talk of all aspects of your condition, treatment, and follow-up" was cited by 72% of the patients. Women with first-time diagnosis reported greater health system/information needs compared to women with recurrent disease [27]. These data highlight the role of dedicated nurses trained to address the complex range of patients' physical and psychosocial problems [13].

Supportive needs also depend on disease extent and cultural environment; advanced stage, symptomatic disease, shorter time since diagnosis, higher distress and younger age predict greater needs.

Many psychological interventions have been proposed, and several studies have been conducted in ABC using different diagnostic tools and therapeutic approaches. A Cochrane review of 1378 patients, randomized in ten clinical trials, explored the impact of psychological interventions, individual or group-based, on psychosocial and survival outcomes. Psychological interventions improved survival at 12 months but not at longer follow-up, and reduced psychological symptoms in only some of the outcomes assessed: i.e. helplessness–hopelessness and social functioning [28]. As outlined by the authors, these findings should be interpreted with caution, and future research is encouraged, as the included trials had reporting or methodological weaknesses and were heterogeneous in terms of interventions and outcome measures.

ABC patients may face isolation from the community of early BC patients, health professionals, and society in general. A recent survey in 158 ABC patients and 146 care-givers in nine European countries – presented in the report called 'The Invisible Woman' – found that $> 50\%$ of patients feel they are perceived negatively by society; many suffer from psychological, physical or financial problems, and only 36% reported support from patient groups [29]. Advocacy organizations (i.e. Europa Donna, METAvivor and the Metastatic Breast Cancer Network in the US, and the Breast Cancer Network in Australia) claim for optimal pain control, psychological support, consideration of patients' perspectives on symptoms, and equal access to supportive/palliative care. They also lobby for increasing research investments (only 5% is currently allocated to ABC) and emphasize the importance of information and multidisciplinary treatment.

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