The Breast 62 (2022) S67–S69

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Unmet challenges in systemic therapy for early stage breast cancer☆

Harold J. Burstein*

Dana-Farber Cancer Institute, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 15 July 2021
Received in revised form
5 December 2021
Accepted 12 December 2021
Available online 13 December 2021

Keywords:
Breast cancer
Early stage treatment
Neoadjuvant
Disparities
Biomarkers

ABSTRACT

Despite marked progress in outcomes for women with early stage breast cancer, unmet challenges persist. These include accounting for the cohort of tumors that do not have favorable clinical outcomes related to tumor heterogeneity, particularly the variation within the subset of ER positive breast cancer; better treatments for subsets where existing therapies are not fully effective; and the development of biomarkers to predict response or need for ongoing treatment. Beyond these tumor-related factors, there is persistent need for focus on improving the patient's experience of treatment – avoiding unnecessary therapy, and providing better supportive care so as to minimize side effects and social and economic disruption caused by treatment. For clinical investigators, the improved prognosis for early stage breast cancer has meant that large sample sizes of subjects are needed for prospective clinical trials with cancer outcome endpoints. As a consequence, the scale of clinical research enterprises has become enormous, too often unsupportable without industry or government resources. Finally, as breast cancer is a global health concern, there is an urgent need to assure that screening and treatment are available to women around the world so that the progress achieved in developed countries can reach billions of women everywhere on earth.

The past 25 years have seen steady improvement in the outcomes for women with early stage breast cancer. Data from the United States indicate that the incidence rate for breast cancer has been remarkably constant since the 1990s; however, the mortality rate has declined nearly 40% over that time span [1]. These gains in survival at the population level are largely attributed to two initiatives in early stage breast cancer: the implementation of widespread screening mammography, and improvements in systemic therapy for early stage breast cancer. Despite such progress, there are many unmet challenges in systemic therapy for early stage breast cancer.

1. Biological variation in breast cancers

Tumor heterogeneity accounts for much of the difference in outcomes among women diagnosed with early stage breast cancer. This variation includes classic subtypes of breast cancer – ER positive, HER2 positive, and triple-negative tumor types – each with its own natural histories and treatment opportunities. But it also describes variations between *any* two cancers, including those within the same histological subtype. Between 5 and 10% of all breast cancers arise from hereditary genetic predisposition, and increasingly, we are testing breast cancer patients for deleterious mutations that indicate unique origins for their tumors [2]. Beyond the inherited genome, tumors themselves possess marked variation in DNA alterations, including mutations, truncations, deletions, and amplifications, which are both clustered by tumor subtype (for instance, ER positive or HER2 positive) but unique to a given cancer [3]. Finally, within tumor subtypes, variations in the patterns of gene expression, as measured by RNA expression signatures, attest to the differences from one breast cancer to another [4]. Superimposed on these genetic and genomic variations between breast cancer are traditional clinical factors such as tumor stage and grade, which retain independent prognostic significance even in the era of molecular characterization of breast cancer [5].

The clinical consequence of this variation in stage and tumor biology is that each individual patient with breast cancer is unique, with a prognosis defined by molecular variations in the tumor, the stage at presentation, and the clinical treatment options. Yet our treatment algorithms and approaches capture only some of that uniqueness. As our ability to individualize treatment based on stage and biology becomes progressively more refined, we have less and

☆ This article is published as part of a supplement supported by St. Gallen Oncology Conferences.

* Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA, 02215, USA
E-mail address: hal_burstein@dfci.harvard.edu.

https://doi.org/10.1016/j.breast.2021.12.009

less data on how, exactly, to care for an individual patient and their cancer. Integrating this extensive and granular data in future clinical trials will be essential to improving systemic therapy for a given patient.

2. Clinically challenging tumor subsets

Some clinical subsets of breast cancer remain particular challenges in modern management. One such subset is luminal B breast cancers, ER positive tumors harboring higher grade features, higher scores on measures of proliferation such as Ki67, with lower levels of hormone receptors, which are typically less responsive to endocrine therapy in the adjuvant setting [6], and often merit neo/adjuvant chemotherapy. Despite the widespread use of chemotherapy and endocrine therapy in the treatment of such tumors, the outcomes remain, on average, less favorable than with luminal A cancers (lower grade, lower measures of proliferation such as Ki67, with higher levels of hormone receptors), treated with endocrine therapy alone. That is, even though luminal B cancers are treated with chemotherapy, chemotherapy does not 'normalize outcomes' in this tumor group or compensate to equalize their natural history [7].

Chemotherapy is also the mainstay of treatment for triple negative tumors. While many triple-negative cancers have an excellent response to neoadjuvant therapy, with complete eradication of the tumor (a 'complete pathological response' or pCR) a substantial fraction of triple-negative cancers do not in fact achieve that benchmark. For patients with residual cancer after neoadjuvant treatment, the risk of recurrence is 4 fold higher than among those with pCR following neoadjuvant therapy. Even in contemporary practice with maximal neo/adjuvant chemotherapy with four agents, paired with immune checkpoint inhibitor therapy, the risk of recurrence for those not achieving pCR approaches 25–50% within 3 years [8]. These findings underscore the need to improve therapeutic options for luminal B and triple-negative breast cancers, as we appear to have reached the limit of what chemotherapy can accomplish for endocrine-resistant or less sensitive tumors.

3. Markers for response and resistance

The use of adjuvant endocrine therapy has been standard in early stage, ER positive breast cancer since the 1990s. To date, however, the only marker to predict benefit from endocrine therapy is expression of ER, itself. Dynamic markers such as change in Ki67 with short, preoperative, window exposures to endocrine therapy may serve as a prognostic marker in ER positive breast cancer, but do not define which patients should or should not receive such treatments [9]. The use of adjuvant anti-HER2 therapy has been standard in early stage, HER2 positive breast cancer since 2005. To date, however, the only marker to predict benefit from anti-HER2 therapy is expression/amplification of HER2, itself. And yet, it is apparent that there is tremendous heterogeneity in the outcomes for ER positive and HER2 positive cancers, despite uniform treatment approaches. Thus, despite decades of research and thousands of studies, we know almost nothing about what predicts lack or response or resistance to the two most widely used classes of targeted therapy in early stage breast cancer. Similarly, we lack any marker of resistance to chemotherapy as a whole, much less specific chemotherapeutic agents. Identifying such markers would be a remarkable discovery that would allow for much more customization of treatment.

4. Challenges to clinical trial designs

Randomized, prospective clinical trials are the engine of progress in systemic therapy for early stage breast cancer. No other cancer condition has been studied as rigorously on a global scale with so many large, randomized studies. The traditional endpoints for defining standards of care have been disease-free or overall survival in the study population, critical landmarks that truly define how a new treatment affects the long-term natural history of the disease. A dilemma for such studies is that to have adequate power to answer key questions in the modern era, clinical trials require hundreds, and more commonly thousands, of study subjects, who are followed for many years. Fundamentally, this is a 'good problem' to have, as it underscores the fact that most women with early stage breast cancer have a very favorable long-term prognosis. But the investment of resources to develop, administer, and analyze such trials is huge, and the operational size of such trials often demands nearly a decade of effort. That scale and timeframe limits the pace of progress in early stage breast cancer.

Consider the outcomes for women with stage 1, ER positive or HER2 positive breast cancers, who account for about 45% of all new diagnoses of early breast cancer in the US. Recent studies have shown cancer free survival on the order of >95% through nearly a decade of follow-up [7,10]. This is marvelous news for patients and a real tribute to the progress in early stage breast cancer. But it poses a practical challenge, because to show 'improvement' in such cohorts of women, clinical trials would likely require more than 20,000 subjects, and 10 years of follow-up.

The lack of a near-term surrogate endpoint that permits a clear definition of improved outcomes in systemic therapy is a critical deficiency in management of early stage breast cancer. The pCR endpoint serves as a strong prognostic marker, but to date, modest improvements in pCR have not translated into clinically meaningful gains in event-free or overall survival [11]. Neoadjuvant therapy may help risk-stratify breast cancer patients, identifying cohorts with greater residual risk, and warranting novel treatment approaches [12]. In some specific situations, typically with lower risk cancers with excellent prognoses and well established outcomes defined by historical controls, it has been possible for single-arm de-escalation trials involving highly effective drugs to define acceptable standards of care [10]. Yet few situations truly lend themselves to such study designs for authoritative use of regimens. Fundamentally, we remain dependent on maturation of randomized clinical trials with event-driven endpoints to define our standards of care. This lack of a robust surrogate marker is a hindrance to faster advances in systemic therapy for early stage breast cancer.

5. Side effects and symptoms of systemic therapy

There has been tremendous progress in supportive care and management of treatment-related side effects resulting from systemic therapy for early stage breast cancer. Improved anti-emetics, white blood cell growth factor support, and hydration have meant that chemotherapy treatment is nearly always delivered in the outpatient setting, with very low risk of infection or hospitalization. Scalp cooling devices now offer the possibility of less alopecia with many chemotherapy regimens, a transformative intervention that may redefine the public image of what it means to be a breast cancer patient. For many women, these innovations have transformed the chemotherapy experience.

And yet, by any measure, the side effects of systemic therapy are profound and overwhelming. Chemotherapy still brings nausea, fatigue, neuropathy, mucositis, and a host of other symptoms, all contributing to a marked decline in physical and psychological

well-being. Endocrine therapies cause menopausal symptoms, arthralgias and osteoporosis, gynecological and sexual health side effects, and other consequences of estrogen deprivation, which often persist for years [6]. Both chemotherapy and endocrine treatments contribute to subtle – and rarely not subtle – neurocognitive issues. It is common for oncologists to say that treatment is 'well tolerated.' Yet such side effects are only 'tolerable' by the accepted norms of cancer care, norms that are tremendous outliers compared to most medical treatments. There is no other disease where such profound consequences of therapy would be considered ordinary. These problems demand on going strategies to optimize care for breast cancer patients.

6. Global disparities in care, access, and outcomes

Breast cancer is a worldwide disease, affecting patients from every country and every social stratum. Indeed, in 2021, breast cancer became the most commonly diagnosed cancer in the world (excepting non-melanoma skin cancers) [13]. As with every clinical disorder, there are profound disparities between countries in the available treatments and related long-term outcomes for management of breast cancer [13]. These gaps reflect lack of access to important, effective drugs, lack of early detection, and variations in epidemiology and public health that predict differences in outcomes. Within countries, there are similar, profound disparities in outcomes for breast cancer, which unfortunately track along familiar, entrenched axes of socioeconomic status and race. More than any new drug, addressing these variations and disparities in outcomes within countries and between countries would contribute immensely to reducing the global burden of breast cancer.

Even within highly developed, affluent societies, the costs of breast cancer care are approaching unsustainable levels. Novel targeted therapies for early stage breast cancer, including those likely to emerge in the next 12 months, now cost between $80,000 and $150,000 for one year of treatment, while household income in the US is $68,000 per family. Such costs make treatment inaccessible to millions of breast cancer patients around the world, and tens of thousands of patients in the most affluent nations. It is clear that the escalating costs of breast cancer therapy now pose a moral challenge to investigators, clinicians, national governments and third-party payers, who are stretched to assure appropriate access for all. Global progress against early stage breast cancer will require different cost and care delivery models if there is to be uniform, accessible, and effective care around the world.

Declaration of competing interest

None.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. Jan CA Cancer J Clin 2021;71(1):7–33. https://doi.org/10.3322/caac.21654. Epub 2021 Jan 12. PMID: 33433946.

[2] Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, Gao C, Lilyquist J, Yadav S, Boddicker NJ, Samara R, Klebba J, Ambrosone CB, Anton-Culver H, Auer P, Bandera EV, Bernstein L, Bertrand KA, Burnside ES, Carter BD, Eliassen H, Gapstur SM, Gaudet M, Haiman C, Hodge JM, Hunter DJ, Jacobs EJ, John EM, Kooperberg C, Kurian AW, Le Marchand L, Lindstroem S, Lindstrom T, Ma H, Neuhausen S, Newcomb PA, O'Brien KM, Olson JE, Ong IM, Pal T, Palmer JR, Patel AV, Reid S, Rosenberg L, Sandler DP, Scott C, Tamimi R, Taylor JA, Trentham-Dietz A, Vachon CM, Weinberg C, Yao S, Ziogas A, Weitzel JN, Goldgar DE, Domchek SM, Nathanson KL, Kraft P, Polley EC, Couch FJ. A population-based study of genes previously implicated in breast cancer. Feb 4 N Engl J Med 2021;384(5):440–51. https://doi.org/10.1056/NEJMoa2005936.Epub2021Jan20. PMID: 33471974.

[3] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Oct 4 Nature 2012;490(7418):61–70. https://doi.org/10.1038/nature11412.Epub2012Sep23. PMID: 23000897; PMCID: PMC3465532.

[4] Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Aug 17 Nature 2000;406(6797):747–52. https://doi.org/10.1038/35021093. PMID: 10963602.

[5] Pagani O, Francis PA, Fleming GF, Walley BA, Viale G, Colleoni M, Láng I, Gómez HL, Tondini C, Pinotti G, Di Leo A, Coates AS, Goldhirsch A, Gelber RD, Regan MM. SOFT and TEXT investigators and international breast cancer study group. Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TEXT and SOFT. Apr 20 J Clin Oncol 2020;38(12):1293–303. https://doi.org/10.1200/JCO.18.01967. Epub 2019 Oct 16. PMID: 31618131; PMCID: PMC7164485.

[6] Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. Reply. Mar 25 N Engl J Med 2021;384(12):1176–7. https://doi.org/10.1056/NEJMc2101282. PMID: 33761226.

[7] Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer Jr CE, Dees EC, Goetz MP, Olson Jr JA, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin PM, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams J, Sledge Jr GW. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. Jul 12 N Engl J Med 2018;379(2):111–21. https://doi.org/10.1056/NEJMoa1804710. Epub 2018 Jun 3. PMID: 29860917; PMCID: PMC6172658.

[8] US Food and Drug Administration. February 9. In: Oncological drugs advisory committee (ODAC) meeting; 2021. Available at: https://www.fda.gov/media/145654/download. [Accessed 22 April 2021].

[9] Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C, Horgan K, Kirwan C, Mallon E, Sibbering M, Skene A, Vidya R, Cheang M, Banerji J, Morden J, Sidhu K, Dodson A, Bliss JM, Dowsett M. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Nov Lancet Oncol 2020;21(11):1443–54. https://doi.org/10.1016/S1470-2045(20)30458-7. Erratum in: Lancet Oncol. 2020 Dec;21(12):e553. PMID: 33152284; PMCID: PMC7606901.

[10] Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, Schneider BP, Shen F, Fuhrman K, Baltay M, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis MJ, Shapira I, Wolff AC, Carey LA, Overmoyer B, Partridge AH, Hudis CA, Krop IE, Burstein HJ, Winer EP. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. Aug 1 J Clin Oncol 2019;37(22):1868–75. https://doi.org/10.1200/JCO.19.00066. Epub 2019 Apr 2. PMID: 30939096; PMCID: PMC7587424.

[11] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer Jr CE, Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Jul 12 Lancet 2014;384(9938):164–72. https://doi.org/10.1016/S0140-6736(13)62422-8. Epub 2014 Feb 14. Erratum in: Lancet. 2019 Mar 9;393(10175):986. PMID: 24529560.

[12] Prowell TM, Beaver JA, Pazdur R. Residual disease after neoadjuvant therapy - developing drugs for high-risk early breast cancer. Feb 14 N Engl J Med 2019;380(7):612–5. https://doi.org/10.1056/NEJMp1900079. PMID: 30763188.

[13] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Feb 4 CA Cancer J Clin 2021. https://doi.org/10.3322/caac.21660. Epub ahead of print. PMID: 33538338.