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Review

New approaches for improving outcomes in breast cancer in Europe

Angelo Di Leo [a, *], Giuseppe Curigliano [b], Véronique Diéras [c], Luca Malorni [a], Christos Sotiriou [d], Charles Swanton [e], Alastair Thompson [f], Andrew Tutt [g], Martine Piccart [h]

[a] Sandro Pitigliani Department of Medical Oncology, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy
[b] European Institute of Oncology, Division of Medical Oncology, Milan, Italy
[c] Department of Clinical Research, Institut Curie, Paris, France
[d] Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[e] Cancer Research UK, London Research Institute, London, UK
[f] Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[g] Breakthrough Breast Cancer Research Centre, Institute of Cancer Research and Kings College London School of Medicine, London, UK
[h] Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Considerable progress has been made in breast cancer treatment in Europe over the past three decades, yet survival rates for metastatic disease remain poor, underlining the need for further advances. While the use of predictive biomarkers for response to systemic therapy could improve drug development efficiency, progress in identifying such markers has been slow. The currently inadequate classification of breast cancer subtypes is a further challenge. Improved understanding of the molecular pathology of the disease has led to the identification of new targets for drug treatment, and evolving classifications should reflect these developments. Further ongoing challenges include difficulties in finding optimal combinations and sequences of systemic therapies, circumventing multidrug resistance and intra-tumor heterogeneity, problems associated with fragmentation in clinical trials and translational research efforts. Adoption of some of the strategies identified in this article may lead to further improvements in outcomes for patients with the disease.

Introduction

Breast cancer is the most common cancer in women worldwide, being responsible for over 500,000 deaths in 2004 [1]. The disease places a considerable burden on patients and healthcare systems, accounting for 10% of overall cancer costs in the European Union [2]. Nevertheless, progress has been made in the treatment of breast cancer in the Western world over the past three decades, with age-standardized, 5-year relative survival rates in Europe increasing from 73% to 83% between 1992 and 2008 [3]. Despite these advances, 5-year relative survival rates for metastatic disease remain poor [4], though the modest improvements in prognosis observed with the advent of modern systemic treatments suggest that more progress could be made as a result of new therapeutic approaches [5–7]. Nonetheless, survival rates for the disease in Europe still lag behind those observed in the United States [8], underlining the need for further advances across the region.

One of the problems facing the medical treatment of breast cancer in Europe is the high cost in the current economic climate. While the use of predictive biomarkers for response to systemic therapy could improve treatment efficacy and reduce costs, progress in identifying such markers has been slow. Additional challenges include the difficulty in finding optimal combinations, sequencing of chemotherapy and biologic therapy, circumventing multidrug resistance and intra-tumor heterogeneity, along with problems associated with disconnects between clinical trials and translational research efforts.

Breast cancer subtypes: evolving definitions and clinical relevance

Invasive breast carcinoma has traditionally been classified according to histomorphologic features into several variants, the

* Corresponding author. Medical Oncology Unit, Hospital of Prato, Istituto Toscano Tumori, 59100 Prato, Italy. Tel.: +39 0574 434766; fax: +39 0574 29798.
E-mail address: adileo@usl4.toscana.it (A. Di Leo).

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most common of which are the ductal and lobular types (reflecting ductal carcinoma in situ [DCIS] and lobular in situ neoplasia, respectively) [9]. Such histologic classifications are currently used in clinical practice along with determination of TNM stage (Tumor size, Nodal involvement, presence of Metastases) to make predictions of disease prognosis [10,11], though they have limited usefulness when selecting the best systemic therapies. More recently, it has become clear that breast tumors are highly heterogeneous in their molecular composition [12], with different subtypes varying in their characteristics and natural history [13–16]. Measurement of these molecular subtypes, which includes determination of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status, and sometimes also the proliferation marker Ki-67, is important since such factors can assist in the estimation of both disease recurrence risk and response to therapy [9]. Receptor status also has an impact on survival, with triple (ER/PgR/HER2) negative breast cancer (TNBC) being associated with the poorest outcome (Table 1) [17].

Breast cancer subtypes can be defined by the use of gene expression microarrays such as Affymetrix GeneChip (Affymetrix, Santa Clara, USA) [18,19] or Illumina (Illumina Inc., San Diego, USA) [20], or by clinical use of gene expression to direct therapeutic decisions: Mammaprint [21], Oncotype DX (Genomic Health Inc., USA) [22], or PAM50 [23]. However, such methods are not commonly undertaken at present due to cost and limited availability, so a simplified approximation to this classification using clinicopathologic determination of ER, PgR and HER2 is often used to help guide treatment selection in clinical practice [24,25]. Such clinicopathologic criteria involve the use of immunohistochemistry (IHC) to assess receptor status and score protein levels semi-quantitatively, while *HER2/neu* gene amplification is evaluated by fluorescent in situ hybridization (FISH). However, use of IHC is not without problems, with quality assurance for interpretation of the results and quantification being particularly challenging [26]. Indeed, such issues have led to sizeable discrepancies between centers in the results of receptor measurements according to central pathology review. As assessment by IHC is now the predominant determinant of treatment for breast cancer, accurate determination of receptor status is crucial since false negatives/positives have an impact on disease management [26]. Consequently, the precise cut-off points for receptor measurement in clinical trials should be considered with care, with protocols following guidelines for the determination of ER, PgR and HER2 [27,28]. Measurement of Ki-67 may be used in order to differentiate between luminal A and B breast cancer and to identify candidates for chemotherapy. Use of Ki-67 measurement remains controversial due to the wide variations in analytical methods employed and lack of quality control; however, such variability is expected to decrease following recent recommendations on pre-analytical and analytical assessment of this marker [29]. Epidermal growth factor receptor (EGFR), cytokeratin (CK) 5/6 expression and other markers can also be measured in order to determine basal subtype in patients with TNBC [25].

Although breast cancer subtypes defined by clinicopathologic criteria are similar to intrinsic subtypes identified by gene expression profiling and represent a useful surrogate definition, they are not identical. Furthermore, this classification of breast cancer subtypes remains suboptimal as a means of directing therapeutic decisions since substantial heterogeneity exists within each molecular subtype, leading to considerable variability in response to therapy. However, it is hoped that molecular subtyping using gene expression profiling will become routine practice after 2015, should the large trials TAILORx (**T**rial **A**ssigning **I**ndividua**L**ized **O**ptions for Treatment [**Rx**]) and MINDACT (**M**icroarray **I**n **N**ode negative **D**isease may **A**void **C**hemo**T**herapy) release 'positive' results, namely that low proliferative luminal cancers can be safely treated with endocrine therapy only. Gene expression profiling has already been endorsed by the latest St Gallen International Breast Cancer Consensus Conference (2013) for making adjuvant therapy decisions [30].

Current treatment options and unmet needs in breast cancer

Multidisciplinary team (MDT) meetings, involving oncologists, surgeons, radiologists, nurses and pathologists, are considered ideal for the management of early breast cancer so that diagnostic and treatment aspects of patient care can be discussed. Indeed, regular MDT meetings are common in Europe, particularly for complex cases, with treatment recommendations being based on national or European guidelines [25,31].

Treatment for breast cancer is dependent on disease stage, histologic and molecular subtypes and menopausal status. Further aspects influencing treatment choice for early breast cancer include balancing the risk of relapse with the benefit of intervention and patient factors such as the impact of treatment on fertility. Surgery (mastectomy or breast-conserving surgery with or without lymph node dissection) and radiotherapy play an important role in early breast cancer: systemic therapy may be used for almost all women and is the predominant treatment for those with advanced disease [25,32]. Tamoxifen, with or without ovarian function suppression, is recommended for premenopausal women with hormone-sensitive (ER+) disease and an aromatase inhibitor (AI) is the preferred option for postmenopausal women. AI therapy can be induced upfront or sequentially by switching from tamoxifen to AI and vice versa

Table 1
Breast cancer receptor subtypes and associated 5-year survival rates. Reproduced with permission from Onitilo et al. 2009 [17].

Characteristic	Overall survival, % (95% CI)	Disease-free survival, % (95% CI)
Subtype		
ER/PgR+, HER2− (luminal A)	90.3% (87.6–92.5)	86.8% (83.8–89.4)
ER/PgR+, HER2+ (luminal B)	88.7% (79.2–94.1)	83.2% (74.0–89.6)
ER/PgR−, HER2+	78.8% (66.0–87.7)	66.0% (53.9–76.3)
ER/PgR−, HER2−	79.0% (70.8–85.3)	73.5% (65.0–80.5)
ER/PgR status		
ER/PgR+	90.1% (87.5–92.2)	86.4% (83.6–88.8)
ER/PgR−	79.0% (72.4–84.4)	70.8% (63.9–76.8)
HER2 status		
Positive	84.6% (77.3–89.9)	75.9% (68.6–81.9)
Negative	88.5% (85.9–90.6)	84.7% (81.9–87.2)
Overall	87.8% (85.4–89.9)	83.1% (80.5–85.5)

CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor; PgR, progesterone receptor.

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