MOLECULAR ONCOLOGY 10 (2016) 1147–1159

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc

Review

Metastatic breast cancer: The Odyssey of personalization

A. Sonnenblick[a,b], N. Pondé[a], M. Piccart[a,*]

[a]Department of Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Boulevard de Waterloo 125, B 1000 Brussels, Belgium

[b]Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

ARTICLE INFO

Article history:
Received 6 May 2016
Received in revised form
27 June 2016
Accepted 5 July 2016
Available online 11 July 2016

Keywords:
Breast cancer
Target therapy
Precision medicine
Biomarkers

ABSTRACT

Metastatic breast cancer is the most frequent cause of cancer death for women worldwide. In the last 15 years, a large number of new agents have entered clinical use, a result of the dramatic increase in our understanding of the molecular underpinnings of metastatic breast cancer. However, while these agents have led to better outcomes, they are also at the root cause of increasing financial pressure on healthcare systems. Moreover, decision making in an era where every year new agents are added to the therapeutic armamentarium has also become a significant challenge for medical oncologists. In the present article, we will provide an ample review on the most recent developments in the field of treatment of the different subtypes of metastatic breast cancer with a critical discussion on the slow progress made in identifying response biomarkers. New hopes in the form of ctDNA monitoring and functional imaging will be presented.

1. Introduction

Breast cancer (BC) is the most common cancer type, as well as the first cause of cancer death among women worldwide, with an estimated 1.7 million new cases and 521,900 deaths in 2012 (Torre et al., 2015). Though most women present with localized potentially curable tumours, incurable and lethal relapses and *de novo* metastatic breast cancer (MBC) remain frequent in clinical practice (Welch et al., 2015).

The classic paradigm of MBC treatment, i.e. decision making that is based on pathological (hormonal receptor status and HER2 status) and clinical (patterns of dissemination, disease burden and presence/absence of symptoms) parameters, that we may call "stratified oncology" has not significantly changed in recent years (Cardoso et al., 2012, 2014). Meanwhile, advances in translational research have generated exponential growth in our understanding of the molecular underpinnings of MBC, including the characterization of molecular subtypes (Perou et al., 2000), discovery of numerous potential therapeutic targets and mechanisms of resistance to treatment (Wang et al., 2011; Stendahl et al., 2004; Pohlmann et al., 2009). Both in parallel and connected to these advances at the bench, in the clinic the therapeutic arsenal available for metastatic patients has increased dramatically.

* *Corresponding author.*
E-mail address: martine.piccart@bordet.be (M. Piccart).

http://dx.doi.org/10.1016/j.molonc.2016.07.002

At the end of the 20th century, available chemotherapy regimens provided a maximum progression free survival (PFS) of 10 months and an overall survival (OS) that rarely exceeded 20 months (Fossati et al., 1998). Later, newer chemotherapeutic agents pushed survival to above 20 months and distinctive indications for sequential versus combined use were developed, with the former becoming the standard, unless response rate was of the essence (Dear et al., 2013). Though recent years have seen a number of new classic cytotoxic agents such as eribulin come into use with positive results, it is the coming of age of targeted therapy, spearheaded by trastuzumab in the late 90s that has transformed and will continue to transform management of MBC in the coming years (Thomas et al., 2007; Mendes et al., 2015; Cortes et al., 2011).

Though "more and better drugs" is one of the paths towards better outcomes, simply adding more drugs does not solve the entire equation. Better matching of drug to patient, through the development of efficient biomarkers – a concept dubbed "personalized" or "precision" medicine – has the potential to both improve results and to reduce unnecessary treatment (and thus toxicity). However, at this juncture, frustratingly and despite intensive research and some hopeful candidates (Lee et al., 2016), the only predicative biomarkers in current clinical use backed by solid evidence remain HER2 and oestrogen receptor status (Table 1). For healthcare systems strained by rising treatment costs (Mariotto et al., 2011), biomarkers may improve the cost-effectiveness of treatment, allowing the adoption of new treatments that would otherwise be considered too costly (Elsada et al., 2016). At the same time, improvements in functional imaging studies may better evaluate both the effect of and response to treatment, allowing for more precise decision making on the part of oncologists than is possible at the present time (van Kruchten et al., 2015).

In the present article, we will provide a review of the essential data that has led to the recent addition of new agents for MBC, discuss new treatment strategies for oligometastatic and overtly metastatic disease, as well as summarize to what extent oncologists can rely on "biomarkers" for the prescription of these expensive drugs.

1.1. *Hormone receptor positive breast cancer*

Hormonotherapy (HT) is arguably the oldest form of target therapy and since the discovery of oestrogen receptor (ER), more than 50 years ago, major advances have occurred in the field (Jensen, 2004) (Table 1). Tamoxifen, a selective oestrogen receptor modulator, was the first compound that showed dramatic responses and a relatively good safety profile in patients with metastatic breast cancer (Ward, 1973). Agents that directly or indirectly target ER by different mechanisms, such as aromatase inhibitors (AI), luteinizing hormone releasing hormones (LHRH) agonists and the ER receptor degrader fulvestrant were also found to be effective in ER-positive breast cancer (Klijn et al., 2001; Mauri et al., 2006). These new agents, added to the drug arsenal in the last decade may be slightly more effective than classic treatments options (Cardoso et al., 2013; Miller et al., 2007). Contrary to chemotherapy, in HT available results do not suggest that association of multiple agents is useful. Three trials evaluating non-steroidal AI (anastrozole) and fulvestrant versus anastrozole alone as first line treatment showed conflicting results. While the SWOG 226 trial showed modest PFS gain of 1.5 months (Hazard ratio [HR] = 0.8, $p = 0.007$) and OS gain of 6.4 months (HR = 0.81, $p = 0.049$) in spite of 41% crossover, both the SOFEA and FACT trials did not show any advantage to the dual combination (Mehta et al., 2012; Bergh et al., 2012; Johnston et al., 2013). Perhaps the efficacy differences are related to the discrepancies in the treated populations between the studies. In the SWOG trial, prior adjuvant tamoxifen was provided to 40% of patients and *de novo* metastasis developed in 38%, while in the FACT trial, prior adjuvant tamoxifen was provided to 66% of patients and *de novo* metastasis developed in only 13%. This suggests that tamoxifen naïve patients without any development of acquired resistance may benefit from dual therapy at first line. Notably, these studies used the suboptimal dosage of fulvestrant 250 mg and not the current optimal dose of 500 mg which showed 20% reduction in risk of progression and was not associated with increased toxicity (Di Leo et al., 2010). Therefore, based on these trials dual anastrozole and fulvestrant is currently not indicated

Table 1 – Current treatment options, biomarkers and future developments.

Subtype	Current treatment options	Available predictive biomarkers	Future developments
ER positive	Tamoxifen	Ooestrogen receptor status	Functional imaging
	Fulvestrant ± Palbociclib	Oestrogen receptor status	Precision medicine trials
	Aromatase inhibitors ± Palbociclib or Everolimus or Trastuzumab (if ER+/HER2+)	Estrogen receptor status	New PI3k inhibitors (ex: buparlisib) Next generation oestrogen degraders (ex: Rad1901)
HER2 positive	Trastuzumab + Chemotherapy	HER2 status	Functional imaging
	Pertuzumab + Trastuzumab + Docetaxel	HER2 status	Precision medicine trials
	TDM-1	HER2 status	
	Lapatinib + Capecitabine or Trastuzumab	HER2 status	
Triple negative breast cancer	Cytotoxic chemotherapy (monotherapy or doublet)	No biomarkers	PARP inhibitors "BRCAness" biomarker
	Bevacizumab + paclitaxel (where approved)	No biomarkers	Precision medicine trials Immunotherapy VEGFA as biomarker of response