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Biomarker Driven Cancer Therapeutics: Existing Tools and Remaining Gaps

Sasi Shanmugam Senga[1*], Jemma Arakelyan[2]

[1]Division of Neuroscience, Australian National University, Canberra, Australia
[2]Department of Oncology, Yerevan State Medical University, Yerevan, Armenia
Email: *authordrsashi@gmail.com, jemmaarakelyan93@gmail.com

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Abstract

Advancements in technology such as proteomics, genomics have led to the concept of personalized medicine wherein the integration of biomarkers into clinic directs cancer therapeutics. Traditional staging has a stochastic element which can only predict the outcome without actual consideration of intrapatient heterogeneity. In this review, we will look at the biomarkers that prove to be valuable tools for the personalization of cancer therapeutics among lung and breast cancer patients.

Subject Areas

Oncology

Keywords

Cancer Biomarkers, Breast Cancer, Lung Cancer

1. Introduction

Breast cancer is one of the most common cancers worldwide and has affected 2.1 million women in the year 2018 alone [1]. While conventional tumour size, lymph node status, and presence or absence of metastasis can direct therapeutics and prognosis, biomarkers give a better picture of an individual's tumour to use targeted therapies.

Breast tumours typically involve multiple driver mutations and evolve over time and specific genomic signatures such as ones arising from mismatch repairs can be useful biomarkers in aiding diagnosis as well as making treatment decisions. A gain of function mutation that leads to an excess of an oncoprotein is a viable target for example amplification of human epidermal growth factor receptor 2 (HER2) than a loss of function (**Figure 1**).

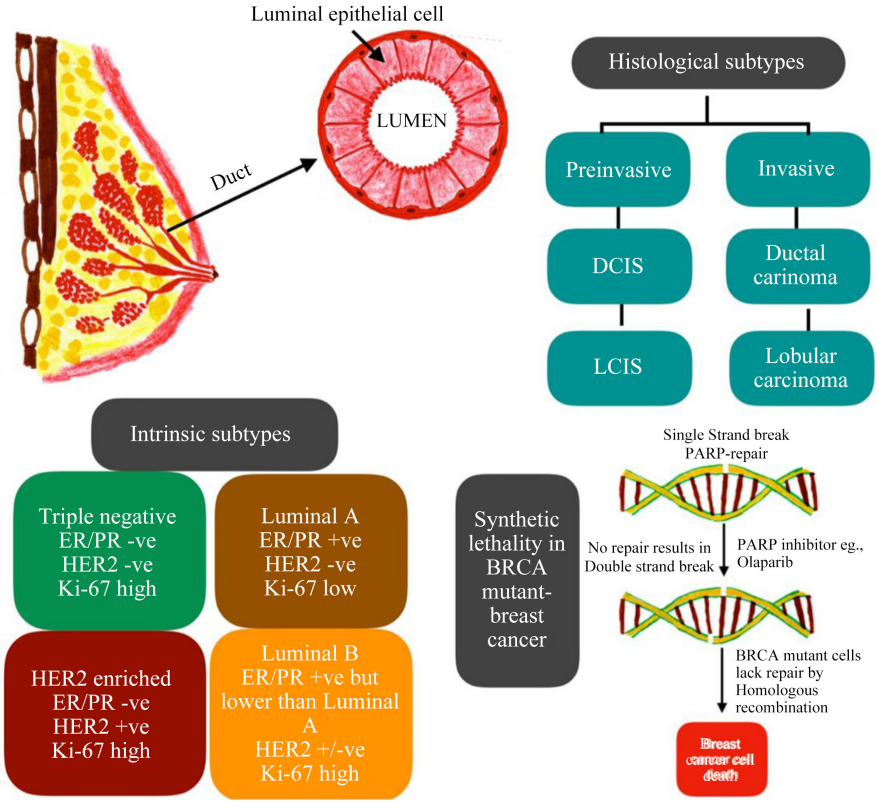

Figure 1. Drawn based on Sims *et al*.; 2007 [24]. Breast Cancer subtypes based on histology and IHC. DCIS-Ductal carcinoma in situ; LCIS-Lobular carcinoma in situ; ER-Estrogen receptor; PR-Progesterone receptor; Ki-67 Proliferation index. BRCA can serve as a biomarker to identify patients who will benefit from PARP inhibitors.

HER2neu receptors

Breast cancers that express HER2 were shown to be highly invasive with features of focal progression and often metastasize to distant organs as such it carried a poor prognosis [2]. It is a pivotal invasive biomarker linked to aggressive disease, and often resistant to chemotherapeutic regimens other than anthracyclines and paclitaxel [3]. But in 1998, following the approval of Trastuzumab [4], the odds of survival has changed drastically along with additional targeted therapies such as Trastuzumab emtansine, Pertuzumab, and lapatinib that have since evolved. HER2 positive breast tumours now carry a much better survival owing to the identification of the biomarker signifying the pivotal nature of biomarkers in cancer therapeutics.

Estrogen receptors (ER)

A vast majority of breast cancers express ER-α positivity. The degree of positivity (score of 0 - 5) and staining intensity (0 - 3) [5] varies, but even in cases with negative results involving tubular or lobular carcinoma, the results must be reconfirmed. As ER positivity is associated with a highly favourable prognosis with the usage of hormonal therapy e.g., Tamoxifen to block estrogen can result

in remission and in ductal carcinoma in situ the recurrence drops by 50% in ER positive cases. Resistance a few years following hormonal therapy is a major challenge, one study has shown rewiring critical regulatory regions via methylation leads to resistance [6].

Progesterone receptor (PR)

PR is positive in about 70% of invasive ductal carcinoma, they are regulated by ER-*α*. PR has been shown to be involved in the reprogramming of ER, acting as a brake of proliferation in ER positive breast cancers [7]. Recurrence is higher in ER positive, PR negative cases than ER positive and PR positive ones. The value of PR positivity in the choice of endocrine treatment has not been proven but a study has shown combined endocrine receptor (CER) score which takes account of both ER and PR status to be a better predictor of disease-free survival than mere IHC of receptor status which will only predict the response to hormonal treatment [8] (**Figure 2**).

Ki-67

IHC assessment of Ki-67 is a measure of proliferative activity. Although the cut-off points are not concordant among various labs, a high proliferative index is Ki-67 levels above 20 regardless of assessment method generally carries a poor prognosis [9].

IHC4 + C score

It incorporates ER, PR status, Ki-67, plus clinicopathological features such as tumour size, nodal status, and grade. A study has shown IHC4 + C can eliminate unwarranted chemotherapy in the adjuvant setting in hormone-positive patients [9].

Depicts breast cancer biomarkers in clinical use and those that are upcoming

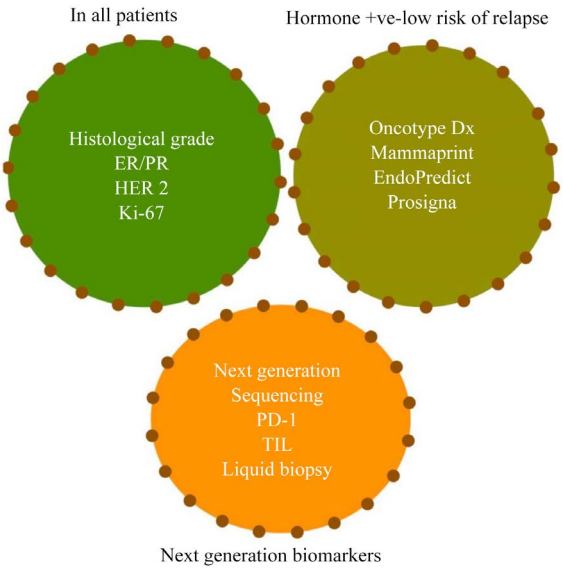

Figure 2. Drawn based on Sims *et al.*, 2007 [24]. TIL-tumour infiltrating lymphocytes; PD-1-Programmed death-1.

Mammaprint

Mammaprint a 70 gene expression assay that quantifies gene expression based on DNA microarray, divides breast carcinoma into high risk and low-risk subtypes.

MINDACT trial by utilizing Mammaprint showed that about 46% of women who were categorized to be of high risk clinically may not benefit from adjuvant chemotherapy if they have a low genomic risk, it led to ASCO approval to give patients with hormone positive, HER-2 negative, 1 to 3 positive lymph nodes with high clinical risk the option to forego adjuvant chemotherapy [10]. An important question is why only hormone positive? Why not hormone negative cancers? The reason is the discriminatory power of Mammaprint is driven by proliferation markers which are unanimously high in ER negative tumours.

Oncotype Dx

Oncotype Dx which tests 21 gene expression has been optimized for use in formalin-fixed tissue. It gives a recurrence score categorizing tumours into low, intermediate and high-risk groups, as per the 2016 ASCO guidelines it is useful in a decision over adjuvant chemotherapy only in node-negative disease [11].

Prosigna (PAM 50)

Utilizes 50 gene signatures to predict the 10-year distant metastasis-free survival in women with node-positive disease who are postmenopausal and hormone-positive. It divides the risk of recurrence into low (score < 40), intermediate (score 40 - 60) and high (score > 60) risk groups [12].

Endopredict (EP)

Based on the expression of 12 genes using RT-PCR (Reverse transcription-polymerase chain reaction) to calculate the risk of recurrence, along with tumour size and nodal status gives a comprehensive risk score and enables stratification of ER positive and HER 2 negative early-stage patients to identify low-risk groups who can be treated with endocrine therapy alone with excellent prognosis without chemotherapy and those who may not need extended adjuvant hormonal therapy [13].

Lung Cancer

Non-Small cell lung cancer (NSCLC) has a plethora of biomarkers that are routinely used clinically to assess disease risk and guide treatment decisions. Despite advancement in therapy, the 5-year survival rate is about 15% [14], due to the presence of advanced disease at the time of initial diagnosis which necessitates early diagnosis (**Table 1**).

MicroRNA miR-33a-5p and miR-128-3p

A study has reported the level of miR-33a-5p and miR-128-3p to be low in the whole blood of lung cancer patients and has been proposed to be used as a biomarker for early diagnosis of lung cancer. miR-33a-5p has been shown to inhibit epithelial to mesenchymal transition in NSCLC and can serve as a prognostic factor [15] [16].

Blood tumour mutational burden

In a less invasive approach to measure tumour mutational burden (TMB) plasma cell-free DNA has been used instead of DNA from tumour tissue to determine lung cancer patients who will benefit from immune checkpoint inhibitors [17], especially checkpoint inhibitors like Pembrolizumab are of immense value to NSCLC patients with metastatic disease who otherwise had a 5 year OS rate of 5.5% [18]. PD-L1 expression-tumour proportion score (TPS) remains the standard biomarker to identify patients who will benefit from immune checkpoint inhibitors despite its shortcomings such as the discordance of PD-L1 expression between primary and metastatic lesion (Figure 3).

Table 1. Depicts lung cancer biomarkers.

Biomarker	Squamous cell carcinoma	Adenocarcinoma	Small cell Lung cancer	Large cell neuroendocrine carcinoma
CEA	↑	↑	↑	↑
PSF3	-	↑ ↑	-	-
Pro GRP	-	-	↑ ↑	-
SCCA	↑ ↑	-	-	-
NSE	-	-	↑ ↑	-
CYFRA 21-1	↑ ↑	-		-
SST	-	-	-	↑ ↑

Adapted based on (Hanash *et al.*, 2018) [25]. CEA-carcinoembryonic antigen; SCCA: Squamos cell carcinoma antigen; NSE: Neuron-specific enolase; SST: Somatostatin.

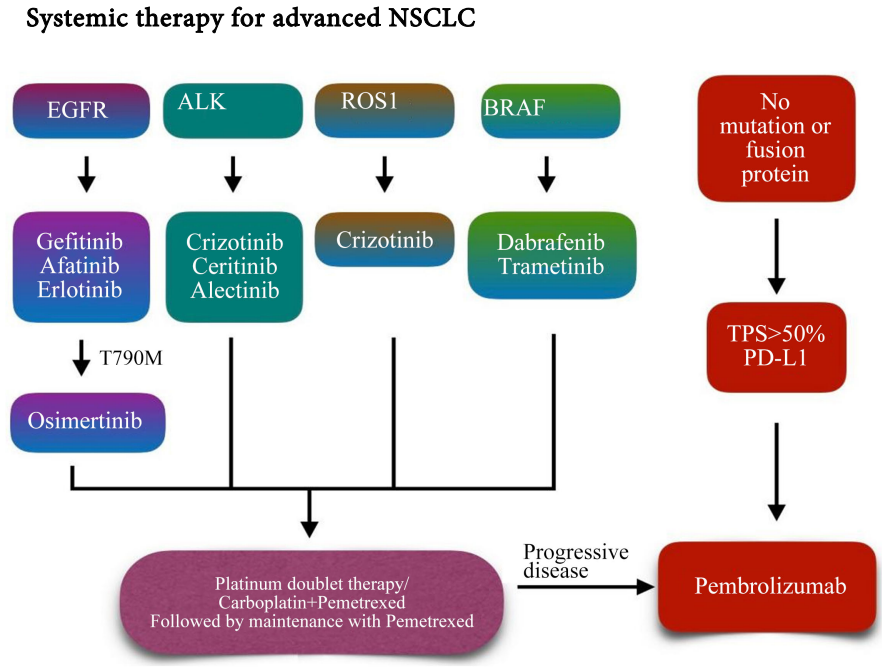

Figure 3. Adapted from Melosky *et al.*; 2018 [26]. Management of NSCLC patients using biomarkers of mutation/fusion proteins; TPS-tumour proportion score.

A study has shown that treatment with Pembrolizumab resulted in a 5 year OS rate > 25% in NSCLC patients with advanced disease who had TPS > 50% [18]. Patients with advanced lung adenocarcinomas are usually tested for *ROS*1 and *ALK* rearrangements, as well as *EGFR* and *BRAF* mutations as their progression-free survival (PFS), increases with targeted therapy.

***Epidermal growth factor receptor* (*EGFR*)**

EGFR mutations generally found in non-smokers with adenocarcinomas possessing lepidic features responds to tyrosine kinase inhibitors (TKI) such as Gefitinib, Afatinib, and Erlotinib. It is important to check for *T*790 mutation in patients who develop resistance to TKI as they will benefit from Osimertinib [19].

***Anaplastic lymphoma kinase* (*ALK*)**

The *EMIA-ALK* fusion is found in a subset of lung adenocarcinoma patients who show a much better response, median PFS 10.9 months with *ALK* inhibitor Crizotinib vs 7 months with conventional chemotherapy [20].

Similarly, Crizotinib has shown to benefit patients with *ROS*1 rearrangements with a response rate of up to 80 [21].

BRAF

Patients with *BRAF V*600*E* mutations are generally smokers and respond poorly to platinum-based chemotherapeutic regimens and carry a poor prognosis but they benefit from *BRAF* inhibitors such as Vemurafenib and Dabrafenib [22].

***Neurotrophic receptor tyrosine kinase* 1 (*NTRK*1)**

In 3% of lung adenocarcinoma patients who harbor *NTRK* fusion a phase 1 studies has reported the benefit of *NTRK* inhibitor, Entrectinib [23].

The exact histological subtyping is pivotal to let patients benefit from such targeted therapies. Diagnostic biomarkers such as thyroid transcription factor (TTF1) and Napsin A are useful in distinguishing poorly differentiated adenocarcinoma from squamous cell carcinoma as it can be quite challenging using only microscopy [19].

2. Prospective

Future studies must focus on biomarkers of cancer prevention and recurrence. ATP citrate lyase cytoplasmic (ACLY) a metabolic enzyme involved in the conversion of mitochondrial-derived citrate into acetyl CoA, a key link between aerobic glycolysis and fatty acid synthesis is gaining traction as an independent predictor of breast cancer recurrence. Increased ACLY has been attributed to poor prognosis both in lung cancer [26] as well as breast cancer [27].

There are a whole array of novel biomarkers along the pipeline, and analysis of circulating free DNA (cfDNA) via non-invasive liquid biopsies confers the advantage of repeated sample collection during the course of treatment enabling detection of new genetic mutations that may emerge such as the *EGFR* Mutation Test v2 (Cobas) which was approved by the FDA in 2016. Even gap junction proteins which are sensitive to injury or disease has been shown to be a potential

biomarker in lung cancers [27], detection of Gap junction beta-4 protein via liquid biopsy has been shown to serve as a novel biomarker to predict chemoresistance in lung cancer [25].

3. Conclusions

Administration of Gefitinib to unselected NSCLC patients did not show any improvement in survival but when the same was administered to those carrying an *EGFR* mutation resulted in a higher response rate signifying the power of biomarker in making therapeutic decisions based on a patient's specific tumour feature.

Herceptin has revolutionized the odds for *HER*2 positive patients who earlier used to carry a very poor prognosis which reiterates the significance of biomarkers as a tool for refining the classification and prognosis of cancer.

As the famous quote by Samuel Coleridge "Water, water, everywhere, Nor any drop to drink", despite the abundance of biomarkers their translation to the clinic has several challenges such as a targeted therapy may be beneficial to the patient but it must also be one that is required continuously for a long-term in order to be a commercial success. Despite evidence of tremendous benefit in targeted therapies based on such biomarkers, their integration from bench to clinic has been challenging. The plethora of promising biomarkers arising from the omics era will change the future of cancer therapeutics from "one size fits all" to individualization.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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