

Short communication

Tailored targeted therapy for all: a realistic and worthwhile objective?

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Introduction

Tailored therapy has become a term popularly used (and misused) with respect to cancer therapy. Everybody spots the difference between having a full tailored suit or dress versus simply cutting the last 5 cm off the legs of some readymade trousers to fit your length. In parallel, tailored therapy should not be confused with implementing simple prognostic or predictive factors. These parameters, in general, do not define direct biological targets, but rather biological parameters revealing a variable statistical correlation to outcome [1]. Taking the analogy of clothes manufacturing, the definition of tailored therapy (made for you) should implement targeted therapies based on identification of individual therapeutic targets such as HER2 in the tumour tissue [2], providing a target exclusive to this tumour for therapeutic attack [3].

In theory, a similar discussion should be applied not only to “targeted” therapy but to anticancer strategies in general, including options like cytotoxic therapy as well. On the one hand, parameters such as the histological grade as well as gene expression profiles revealed by microarrays provide moderate statistical correlates to outcome [4] but do not define biological targets. In contrast, a parameter such as topoisomerase II may be considered borderline in this respect. The fact that this enzyme is a direct target of anthracyclines, and amplification of its gene has been related to improved sensitivity to anthracycline therapy [5,6], suggests anthracycline-based chemotherapy to be a tailored therapy for topoisomerase-II-amplified tumours. On the other hand, topoisomerase II overexpression is not mandatory for anthracycline response, and evidence regarding its predictive role remains conflicting [7].

In the present article we will briefly go through the potential for tailored treatment in breast cancer. As may be seen, most

breast cancer patients already receive some form of tailored therapy, and recent evidence suggests novel highly innovative tailored approaches to be on their way into the clinic.

Breast cancer taxonomy

It is conventional wisdom that breast cancers may be separated into two categories – so-called oestrogen receptor (ER)-positive tumours versus ER-negative tumours. What remains more controversial is the exact definition of receptor positivity; should we consider 1% or 10% of cells expressing positive staining as the lower limit, and should staining intensity be taken into account [8]?

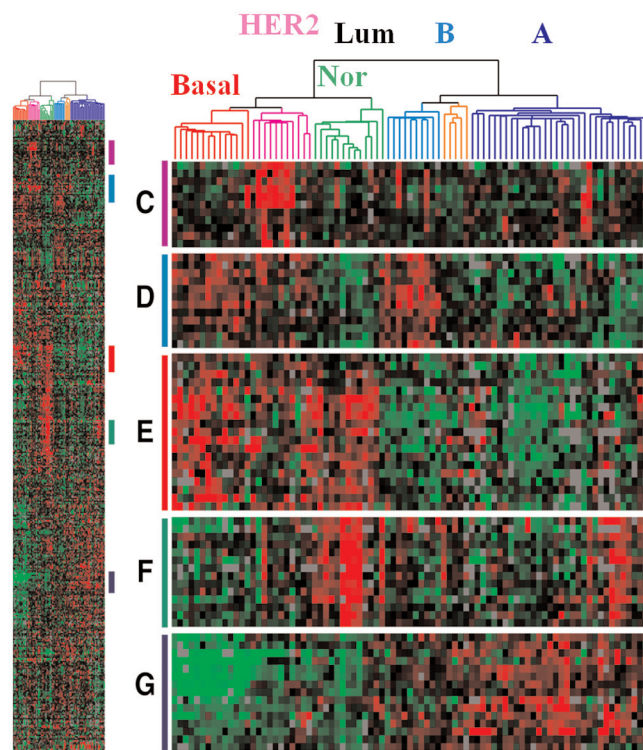
Breast cancers have more recently been separated into five distinct classes based on gene expression profiles (Figure 1): the luminal A and luminal B classes, the HER2 and basal classes, and, finally, so-called normal breast-like tumours [9]. The different tumour categories express distinct gene expression profiles; in addition, the different classes reveal different prognoses [9,10]. While the different classes do not predict responsiveness to anthracycline-based or mitomycin-based chemotherapy [11], tumours belonging to the different classes may be subject to different targeted, or tailored, therapeutic approaches. The following discussion on targeted therapy will therefore be based on this classification.

Luminal A and luminal B tumours

While revealing certain differences regarding gene expression profiles, the luminal A and luminal B classes together harbour tumours expressing the ER. It is now well established that antihormonal therapy (either with use of anti-oestrogens or through oestrogen suppression) works by depriving tumour cells of ligand ER activation; therefore the fact that endocrine therapy may work only among tumours expressing the ER [12] reveals endocrine therapy based on ER assessment actually to be the first as well as the most used

ER = oestrogen receptor; PARP = poly(ADP-ribose) polymerase.

Figure 1



Classes of breast cancer based on gene expression profiles. Gene expression pattern of 85 experiment samples representing 78 carcinomas, three benign tumours and four normal tissues. Basal, basal-like cell class; HER2, HER2 class; Nor, normal cell-like class; LUM B A, luminal B and luminal A classes, respectively. Note: in the initial work light blue was termed luminal C class while yellow was luminal B – these two classes together now are grouped as luminal B. Adapted from [9].

tailored therapy in oncology. The fact that many ER-positive tumours do not benefit from endocrine therapy [13] resembles what is observed with respect to other targeted therapies as well [3], and may be due to potential disturbances in other genes involved in complex downstream pathways [14-16].

In conclusion, endocrine therapy fulfils the definition of a tailored therapy: depriving ER-positive breast cancer cells of their oestrogen ligand stimulation has dramatic effects on cell growth [17], and contemporary adjuvant therapy for ER-positive breast cancer reduces the relapse rate by >30% [12]. In general, tumours belonging to the luminal A class express the ER to a higher level as compared with tumours belonging to the luminal B class, and indirect evidence suggests tamoxifen to be more effective among luminal A tumours as compared with luminal B tumours [10]. Interestingly, recent evidence has suggested HER2 may play a role to endocrine resistance in some ER-positive tumours not amplified for the HER2 gene (see below). The fragile side of tailored endocrine therapy, like all other anticancer

therapeutics, lies in the fact that we (in contrast to the tailor) do not understand all measures to be taken to create the perfect fit; we do not understand the mechanism of therapy resistance. This lack of knowledge is illustrated by the fact that the majority of ER-positive breast cancers are not cured in the adjuvant setting, as well as the fact that endocrine treatment of metastatic disease (like all other therapeutic manoeuvres in this setting) remains palliative.

HER2 class tumours

These tumours in general are characterized by over-expression of a variable number of genes located on the same amplicon as HER2. Tailored therapy for these patients should be separated into two topics: the role of HER2 targeting, and the potential predictive role of the HER2 class (or amplification of certain genes within this class) as predictive factors for chemotherapy sensitivity.

Proof of concept for the therapeutic benefit of targeting HER2 with trastuzumab was revealed in metastatic disease [18]. While response rates were modest and of limited duration, implementation of trastuzumab in concert with chemotherapy provided dramatic benefits in the adjuvant setting [3,19]. Notably, effective anti-HER2 therapy is not limited to trastuzumab; such effects may be achieved with different tyrosine kinase inhibitors preventing HER2 activation [20,21]. Interestingly, recent evidence now suggests that lapatinib and trastuzumab administered in concert may improve outcome as compared with lapatinib monotherapy in cases of trastuzumab failure [22]; there is also evidence that lapatinib may improve efficacy of aromatase inhibition for patients harbouring ER-positive tumours nonamplified for HER2 failing tamoxifen treatment [23]. Interestingly, treatment with aromatase inhibitors has been shown to upregulate HER2 expression in HER2 nonamplified tumours [24]. While the mechanisms of resistance to endocrine therapy remains complex [25], these data suggest a possibility to circumvent this resistance, at least in some patients. The biological characterization of these mechanisms and the potential for upfront identification of patients benefiting from combined treatment, however, remain to be elucidated.

A second issue relates to chemotherapy regimen selection. There are several studies revealing a dose-response benefit for anthracyclines in HER2-overexpressing tumours not detected among tumours expressing HER2 at normal levels [26-28]. This effect has been related to co-amplification of topoisomerase II [5,6,29], located on the HER2 amplicon. These results, however, have not been consistently reproduced [7]. HER2 and topoisomerase II are located on chromosome 17, which in addition harbours several other genes involved in processes like DNA repair and apoptosis. Trisomy of this chromosome occurs in many breast cancers, and some studies have actually suggested chromosome 17 trisomy to be a better predictor of anthracycline sensitivity as compared with HER2 or topoisomerase II amplification [30,31].

In conclusion, tailored therapy targeting HER2 is an established treatment option in breast cancer, and recent evidence suggests an extended role for such strategies in the future. While much evidence suggests a correlation between HER2 amplification and sensitivity to anthracyclines, we lack a complete understanding of the mechanisms involved.

Basal-like tumours

The basal-like tumours are characterized by a particular gene expression profile, in general lacking expression of the ER as well as the progesterone receptor and HER2. While the term triple-negative breast cancer has come into common use, it should not be used synonymously with the term basal-like breast cancer. Tumours of the basal-like class may account for about 60 to 80% of all triple-negative tumours only [32,33], the residual in general belonging to the so-called normal breast-like class.

Gene expression profiles suggest most tumours arising in BRCA1 mutation carriers to belong to the basal class [10]. While probably around 10% of all basal-like tumours arise in BRCA1 mutation carriers [34], there is evidence suggesting that many more basal-like tumours may harbour disturbances in the BRCA1 pathway [35]. In contrast, no distinct gene expression profile for BRCA2 mutated tumours has been identified. BRCA1 as well as BRCA2 mutated tumours harbour defects in homologous repair, one of the key DNA repair pathways in response to double-strand DNA breaks [36]. This leads to development of poly(ADP-ribose) polymerase (PARP) inhibitors preventing DNA repair through alternative pathways [37]. These drugs should therefore work selectively against tumour cells harbouring these defects. Indeed, use of PARP inhibitors as monotherapy has revealed objective responses in metastatic breast carcinomas [38] as well as in ovarian carcinomas [39]. In addition, when metastatic breast cancer patients were treated with a gemcitabine/carboplatin regimen with or without a PARP inhibitor [40], addition of the inhibitor improved the clinical benefit rate as well as improving progression-free survival and overall survival. Most interestingly, the patients in this study were not enrolled subject to BRCA1/BRCA2 testing but based on a triple-negative status. These findings add support to the hypothesis that many basal tumours harbour defects in the BRCA1 pathway of homologous repair, and suggest an extended potential for PARP inhibitors.

In conclusion, use of PARP inhibitors is at an early stage; however, the results obtained are encouraging with respect to monotherapy as well as an adjuvant in concert with chemotherapy. The findings that such drugs may work in triple-negative tumours on a wider scale suggest a therapeutic potential beyond use in tumours with defined BRCA1/BRCA2 mutations, although further research in this area is warranted.

Normal breast-like class

The incidence of these tumours varies across different studies [10], and we lack a clear understanding of their

biology. Notably, tumours of this class seem to carry a poor prognosis not much different from tumours belonging to the luminal B class as well as the basal-like cell class [9], indicating their normal-like gene profile not to be a good prognostic sign. Based on the results obtained with PARP inhibition among triple-negative tumours [40], one may speculate whether some of these tumours may actually harbour defects in homologous DNA repair – a subject to be explored in future studies.

Conclusion

Starting out as a nonselective therapy a century ago [41], following the identification of the ER as a predictive marker, endocrine therapy in breast cancer has been the ultimate targeted, or tailored, cancer therapy for three decades. Over the past decade, tailored therapy with use of anti-HER2 strategies has revolutionized treatment for approximately one-fifth of breast cancer patients. With the introduction of the PARP inhibitors, we are now in the process of tailoring treatment for patients carrying BRCA1 and BRCA2 defect tumours – and probably also for many additional patients carrying triple-negative tumours. Although much more research in this area is warranted, the results achieved up to now suggest tailored therapy for most, if not all, breast cancer patients in need of systemic treatment may become a realistic approach in the near future.

Competing interests

The author declares that they have no competing interests.

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