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On the road to precision, there is more practical medicine to be implemented

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ABSTRACT

Estimates are that of the annual global burden of 1.5 million new cases of breast cancer, two-thirds have hormone receptor positive tumors; a majority of these women come from low- and middle-income countries. For adjuvant patients with hormone receptor positive tumors, a major goal is identification of a "precision medicine", implying a genomic, test whose application will allow identification of those whose systemic treatment can be hormonal therapy alone. Such tests in current use are very expensive and thus in the foreseeable future are out of reach of most women who pay out of pocket.

For some time it has been evident that quantitative scoring of tumors for intensity and prevalence of tumor-cell staining for estrogen or progesterone receptor (ER or PR) expression (the commonest system was first described by Allred and thus provides "Allred" scores) gives an inexpensive measure of likelihood of response to hormonal therapies – a different predictive, precision medicine tool. Majorities of hormone receptor positive tumors (one third of all patients) have "Allred" scores of 6–8 (versus scores of 3–5) for both ER and PR and these tumor-bearing patients benefit significantly more from hormonal treatments than their lowering scoring-afflicted women. When ER and PR quantitative intensity and prevalence scoring is combined with Her-2/neu testing and careful tumor histologic grading, luminal A and B type tumors can be well-defined and gene-expression testing adds little practical predictive information.

For women with hormone receptor positive tumors, high quality, cost-effective "precision medicine" is available without tumor gene-expression testing.

"Give them the third best to go on with; the second best comes too late, the best never comes."

Robert Watson-Watt

A major goal for defining optimal adjuvant therapy for women with operable breast cancer is identifying a treatment(s) which can achieve population impact. As for other cancer clinical trials, the majority of data in this search have been developed from investigations involving women from high-income countries, and these data have impacted high-income country populations favorably [1]. However the majority of new annual global cases now occur among women from low- and middle-income counties (LMIC); and half of all global cases now occur in LMIC premenopausal women [2]. For this communication, the relevant epidemiologic bottom line is that one third of annual new global cases of breast cancer are hormone receptor positive premenopausal cases – approximately 500,000 cases annually, and another 12% are hormone receptor positive postmenopausal cases-approximately 175,000 in LMIC inhabitants, for a total of 675,000 of 1 million LMIC cases, or 45% of all global annual cases. For these LMIC women in particular three general observations obtain about the treatments they may actually receive. First, costs-of-pharmaceuticals and tests-issues are a major barrier to seeking, beginning and completing any adjuvant therapy program because women are usually paying for these expenses out of pocket. Second, chemotherapy treatments, often considered the first and only option, because of high-income country guidelines, are usually of basic; regimens—CMF, CEF or CAF* and because of toxicity and practicality problems, are given in reduced doses and on irregular schedules with uncertain, but likely lower-than-achievable levels of benefit in *CMF = cyclophosphamide, methotrexate, 5 fluorouracil; CEF = cyclophosphamide, epirubicin, 5 fluorouracil; CAF cyclophosphamide, doxorubicin, 5 fluorouracil premenopausal women and marginal benefit in postmenopausal women [3,4]. The general

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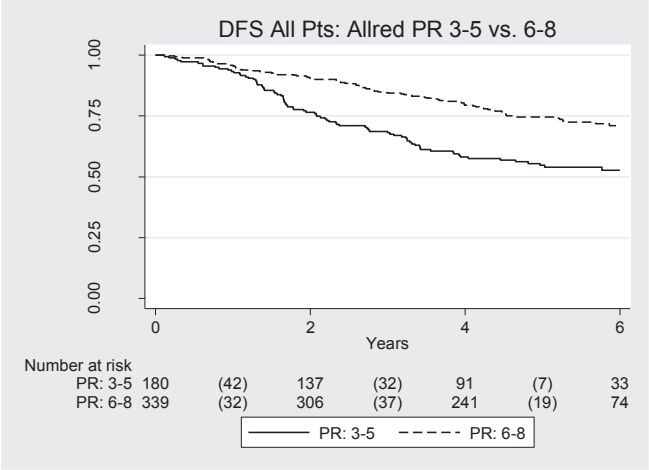
phenomenon of an inverse relationship between benefit from chemotherapy and positive hormonal receptor status makes this situation even more relevant [4]. Third, hormonal therapies are significantly underused in LMIC. Again western country guidelines play a role in this, but testing for presence of hormonal receptors and details of benefits are poorly understood.

With this background, the issue of selection of cost-effective approaches to management of women with hormonal receptor positive tumors is a major one globally. Further specifically, the state-of-the-art for tumor gene-expression profiling for selection of patients who can benefit from hormonal therapy alone deserves particular attention when such profiling—allowing "precision medicine" – is increasingly suggested to be the most scientific and rigorous approach [5]. This communication reviews evidence which suggests that in fact use of standard immuno-histochemical (IHC) assays for assessment of quantitative intensity and prevalence scoring for estrogen and progesterone receptor expression, combined with an IHC assay for Her-2/neu overexpression, and careful histological tumor grading, can well identify patients with luminal A type tumors for whom hormonal therapy alone is optimal adjuvant treatment, as well as those patients for whom other therapies (trastuzumab and/or chemotherapies) additionally are more likely to be beneficial. When these much-less-expensive and usually-performed tests are used thoughtfully, instead of gene-expression testing, "precision", high quality, and cost effective medicine can be provided to the global majority of women needing such care.

Standardized hormonal receptor testing is well-defined and quantitative intensity and prevalence scoring for levels of estrogen receptor and progesterone receptor expression are clearly predictive of response to hormonal therapies

ASCO and the College of American Pathologists have developed comprehensive documents describing how quantitative ER, PR and Her-2/neu tumor data can be replicably obtained through standardized and relatively inexpensive procedures [6,7]. A recent critical review strongly supported such quantitative determinations [8]. These guidelines clearly recommend reporting of percentages of cells staining positively for ER and PR and intensity of the staining and cite the seminal papers of Harvey et al. and Moshin et al. which defined the significant clinical relevance and used the mostly widely applied system subsequently – the "Allred" system [6,9,10]. Specifically in this system a proportion score is assigned, which represents the estimated proportion of positive-staining tumor cells (0, none; 1, <1/100; 2, 1/100 to 1/10; 3, 1/10 to 1/3; 4, 1/3; to 2/3; and 5, >2/3). Next, an intensity score is assigned, which represented the average intensity of positive tumor cells (0, none; 1, weak, 2, intermediate; and 3, strong). The proportion and intensity scores are then added to obtain a total score, which ranges from 0 to 8 [9].

From the publications of Harvey and Mohsin the predictive association of levels of increasing ER and PR by Allred scores respectively and better outcomes from adjuvant hormonal therapies have been demonstrated [9,10]. The remarkable impact of higher PR scores in particular is shown in Fig. 1, which was observed in patients treated with adjuvant surgical oophorectomy and tamoxifen [11]. The importance of PR receptor expression has been confirmed in another study by Prat et al. in which in luminal A type cancers, greater PR IHC prevalence, and higher rates of gene and protein expression were observed [12]. Similar, slightly less impact of higher ER scores was observed in the patient study from which Fig. 1 data come [13]. As in previous studies, these observations are not to negate some benefit from hormonal therapies to patients with lower scores [9,10].



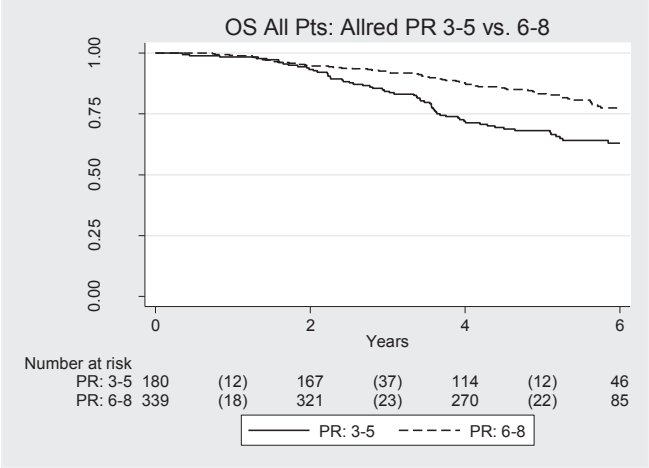


Fig. 1. a and b: Disease-free and overall survival in 519 premenopausal hormone receptor positive patients treated with surgical oophorectomy and tamoxifen according to their tumor progesterone receptor Allred scores [11] (see text for definition of Allred scores).

Majorities of breast tumors are luminal A type (ER+, PR+/–, Her-2neu), but types and subtypes vary across populations

Intrinsic luminal A subtype breast cancers identified by gene expression analysis are variously ER positive, Her-2/neu overexpression negative, and PR positive or negative, or with these characteristics and low Ki-67 (<14%) [14,15]. The data about predictive capacity of luminal A status seems clearer with ER negative tumors, which across populations is the subgroup with the majority of hormonal receptor positive cases [11,14,16]. In a moderate sized (<500 total cases) American population-based series, ER+, PR+/–, Her2/neu– cases accounted for 50–60% of all cases [14]. African American race and premenopausal status were associated with lower frequencies of luminal A tumors in this study. 70% of luminal A cases were both ER+ and PR+. If three quarters of these cases were ER6-8, and PR6-8 (the approximate distribution seen in the clinical trial data shown in Fig. 1) then on population basis 25% of all pre- and postmenopausal cases might be ER6-8, PR6-8, Her-2/neu negative and strongly responsive to hormonal therapies [8–11].

In the adjuvant trial whose data are shown in Fig. 1, at the main Filipino recruiting hospital, of all premenopausal women approached 70% had HR+ tumors [11]. In this study, 87% of HR+ tumors were ER+PR+, and ~80% were ER+PR+Her-2– luminal A. Of these 80% 2/3rds or 53% were ER6-8, PR6-8. Thus on a population basis for 1000