An unmet need: tailoring extended adjuvant endocrine therapy

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Should every woman with a hormone-receptor-positive breast cancer receive endocrine adjuvant therapy for ≥10 years? The question is becoming very relevant in the light of the recently reported results of two large randomised trials demonstrating that 10 years of adjuvant tamoxifen produced a small but significant reduction of recurrences and deaths compared with the conventional duration of 5 years only (Davies et al, 2013; Gray et al, 2013). The results are in agreement with the well-characterised feature of hormone-receptor-positive tumours that carry long lasting risk of relapse persisting for more than a decade (Early Breast Cancer Trialists’ Collaborative G, 2011; Dowsett et al, 2010). They also fit very well with the findings that extended endocrine treatment with aromatase inhibitors after 5 years of tamoxifen led to a significant reduction of risk of relapse (more than 40%) and death (Jakesz et al, 2007; Mamounas et al, 2008; Jin et al, 2012). However, no matter how large, the benefit of extended endocrine treatment is restricted to a fraction of the patients’ population and must be weighted against the side effects of such prolonged chronic therapy (Muss et al, 2008; Amir et al, 2011; Davies et al, 2013). The identification of patients who will benefit from extended endocrine treatment is therefore very relevant to tailor the prescription of tamoxifen or aromatase inhibitors beyond 5 years and to avoid it in patients who will not derive additional benefit.

In their recent paper, Dubsky et al (2013) explored the prognostic value of the EndoPredict (EP) score for early (0–5 years) and late (>5) distant recurrences in 1702 postmenopausal women with ER+ /HER2− breast cancer treated with adjuvant endocrine treatment (tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years). Their findings may be relevant to the need of tailoring extended endocrine therapy. EP is one of several multigene assays (i.e., Recurrence Score, 70-gene signature, PAM50, Breast Cancer Index) developed to identify among patients with estrogen receptor-positive, HER2-negative tumours treated with endocrine therapy those carrying a risk of relapse low enough to avoid chemotherapy (Paik et al, 2004; Buyse et al, 2006; Parker et al, 2009; Filipits et al, 2011; Jerevall et al, 2011). Because the purpose of these signatures was to define the overall risk of recurrence at 10 years, until recently their potential time- lasting prognostic value (i.e., the different prognostic value over time) has only occasionally been reported (Albain et al, 2010; Nielsen et al, 2010).

In their work, Dubsky et al (2013) analysed the time- varying value of EP in the same series of cases that they had already used to validate the assay (Filipits et al, 2011). They therefore report a secondary and unplanned analysis. In patients treated with 5 years of adjuvant tamoxifen, the high EP group had a higher risk of early (HR = 2.73, P < 0.001) as well as late relapse (HR = 2.87, P = 0.013). The EP score retained significance in multivariate analysis adjusted for clinico-pathological variables. In the group with low EP, the risk of distant event in the interval from 5 to 10 years was 3.71% (0.89–6.52%). However, extended endocrine treatment does not only reduce the risk of distant events but it is also capable of decreasing local, locoregional and contralateral events (Goss et al, 2003; Davies et al, 2013), all measures of benefit that must be taken into account when deciding about the opportunity of prescribing prolonged hormonal therapy.

The analysis performed by Dubsky et al (2013) was not limited to the multigene assay. They confirmed that tumour size and nodal status maintain their role of prognostic factors linked to the risk of early and late relapse independently from molecular markers (Bianchini et al, 2013; Dubsky et al, 2013; Sestak et al, 2013; Sgroi et al, 2013b). The combination of clinico-pathological variables and molecular assays should therefore improve the prognostic performance of either assessment alone (Pusztai, 2011). In keeping with such concept, Dubsky et al (2013) showed that a combined score, including EP, nodal status and tumour size (EPclin), performed very powerfully in defining a low-risk group associated with only 1.8% probability of distant metastasis from year 5 to 10. However, the group of patients defined by pathological variable in whom the assay is really informative, therapeutically relevant and clinically useful remains to be defined. For instance, in node-positive tumours the group with low EP may be at lower but still appreciable risk of relapse.
The absolute benefit from extended endocrine therapy is the result of the combination of the size of the risk of relapse and the extent of the relative treatment benefit. If a marker is purely prognostic, the relative treatment benefit is the same for each marker value and therefore the absolute benefit from a treatment is expected to increase proportionally with the increased risk of relapse. This is likely true for nodal status and tumour size. For markers that are both prognostic and predictive the absolute benefit is not necessarily correlated with the risk. This applies to many context-specific predictors, including the EP score, which was optimised to predict the risk of relapse in the context of patients treated with tamoxifen and is based on a combination of genes related to proliferation and ER signaling (Filipits et al, 2011). Even if the prognostic and predictive contribution to the prediction of risk by the EP score has not been formally characterised, the high-risk group defined by the assay is likely represented by patients with poorer prognosis (high proliferation) and deriving relatively low benefit from tamoxifen (low ER signaling). Indeed, there are several studies indicating the association between high ER protein and gene expression, and ER-related genes expression with benefit from tamoxifen and AIs (Bartlett et al, 2011; Early Breast Cancer Trialists’ Collaborative G, 2011; Kim et al, 2011). The ambiguity of the EP score is in the fact that patients who should avoid extended adjuvant treatment are not only those at low risk of relapse (low EP category) but also those with low likelihood of benefit from the treatment, who are expected to fall particularly into the high-risk category of EP. In addition, patients with high ER signaling and low EP category could still derive major benefit from extended endocrine therapy in spite of the lower risk. All the above underscore the need for caution before the clinical implementation of molecular assays for decision making about extended endocrine therapy and call for in-depth investigation of their prognostic and predictive value.

Recently, other gene-expression signatures originally developed for tailoring administration of adjuvant chemotherapy to ER-positive/HER2-negative breast cancer patients treated with endocrine therapy were assessed for their ability to predict early and late relapses (Table 1) (Sestak et al, 2013; Zhang et al, 2013; Sgroi et al, 2013a, b). Similar considerations as discussed above for EP also apply to these markers. Interestingly, some molecular markers (i.e., proliferation markers, Oncotype DX, IHC4) showed a significant time-varying prognostic value (Sestak et al, 2013; Sgroi et al, 2013b). Overall, these studies provided strong support to two key concepts. The first is that primary tumour samples collected at diagnosis can provide information on the clinical course of the disease that has prognostic value even at late intervals. In an effort to investigate how to use the molecular information of the initial diagnosis to define the time-varying risk of relapse, we investigated whether a different combination of proliferation markers and ER-related genes could improve the prediction of early and late relapses (Bianchini et al, 2013). A significant interaction between proliferation and ER-related gene was present in cases that relapsed late. In low proliferation tumours, a low expression of ER-related gene was associated with a higher risk of late relapse. The observation is in agreement with the findings of Dubsky et al (2013), given that low proliferation tumours (only 4% were high grade) were preferentially included in their study. Conversely, in high proliferation tumours, the group with high expression of ER-related genes was associated with low rates of relapse in the early period but with a high risk of relapse in the late period. Patients with tumours that follow within the category of high proliferation and high expression of ER genes could therefore be the ideal candidate to extended endocrine treatment, and the data warrant independent confirmation.

Meanwhile, it is appropriate not only to suggest caution in the application of molecular features and gene expression scores for tailoring extended endocrine therapy but also to encourage continuous research. The findings available so far, including the work of Dubsky et al (2013), suggest that the field is moving in the right direction.

Table 1. Summary of studies investigating the risk of late relapse by molecular assays

| References       | Endocrine treatment                         | Patient population                           | Nodal status                  | Biomarker assessed                        | Group at high risk for late relapse |
|------------------|---------------------------------------------|----------------------------------------------|-------------------------------|-------------------------------------------|-------------------------------------|
| Dubsky et al, 2013 | Tamoxifen or tamoxifen followed by anastrozole | ABCSG-06                                     | Node negative and positive (96% G1 or G2) | EndoPredict (EP) EPclin (including tumour size and nodal status) | High EP High EPclin |
| Bianchini et al, 2013 | Tamoxifen                                    | Public data sets                             | Node negative and positive    | Combination of proliferation (MKS, GGI) and estrogen-related genes (ERS) markers | High-proliferation/ high ERS Low-proliferation/low ERS |
| Zhang et al, 2013  | Tamoxifen (2 or 5 years)                     | Stockholm TAM and institutional cohorts       | Node negative                 | Breast Cancer Index (BCI) (linear combination model) | Intermediate/high BCI |
| Sgroi et al, 2013b | Tamoxifen or anastrozole                     | ATAC                                         | Node negative                 | BCI (linear combination model) HOXB13/IL17BR (H/I) MGI IHC4 RS | Intermediate/high BCI High HOXB13/IL17BR (H/I) |
| Sgroi et al, 2013a | Tamoxifen                                    | MA.17                                        | Node negative and positive    | HOXB13/IL17BR (H/I)                       | High HOXB13/IL17BR (H/I) |
| Sestak et al, 2013 | Tamoxifen or anastrozole                     | ATAC                                         | Node negative and positive    | IHC4 RS ROR (from PAM50)                  | High ROR |

Abbreviations: ERclin = combined EndoPredict and clinical variables; GGI = Genomic Grade Index (MapQuart Dx); HOXB13/IL17BR (H/I) = homebox B13/interleukin 17 receptor B two-gene ratio; IHC4 = combination of four immunohistochemical markers; MGI = Molecular Grade Index; MKS = Mitotic Kinase Score; ROR = Risk Of Recurrence (Prosigna); RS = Recurrence Score (Oncotype DX).
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