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Abstracts

Breast cancer

UPFRONT AROMATASE INHIBITORS (AI) IN EARLY BREAST CANCER: AGAINST

F. Boccardo, P. Guglielmini, A. Rubagotti. *Department of Medical Oncology, University and National Cancer Research Institute, Genoa, Italy*

While several large trials have now established that AI are more effective than tamoxifen (T) when used as adjuvant endocrine therapy, the optimal adjuvant strategy, in particular whether AI should replace T from the beginning or after a few years of T treatment, remains a matter of debate.

For some Authors, upfront use of an AI offers the best opportunity to reduce the risk of early relapse, within the first 2–2.5 years after surgery, for post-menopausal patients likely to harbour tumours primarily resistant to T.[1] There is some evidence that HER2-overexpressing, low level of ER or PGR-negative tumours might be less responsive to T and better suited to treatment with AI at the onset.[2] In the more recent analysis of the ATAC trial, at a median follow-up time of 100 months, there was no significant heterogeneity across the treatment subgroups, except for the small subgroup of ER-positive and PgR-negative patients for whom the benefit in favour of anastrozole appeared to be greater.[3] However, this finding, has not been confirmed by the BIG 1–98 trial data.[4] Moreover, a retrospective analysis of the ATAC data performed by Dowsett and coll. and focused on the relationship between centrally tested, quantitative ER and PgR and HER-2 status, with cancer recurrence, did not identify patients with differential relative benefit from anastrozole over T.[5]

In looking at the early relapse curves of the ATAC trial relative to the women given T alone, one should also consider that, in this cohort, about 70% of women were node-negative and did not receive any adjuvant chemotherapy (CT), as they probably would do nowadays, according to more recent guidelines.[6,7] The most recent results of the EBCTCG metanalysis and those of several individual trials provide a clear evidence that the addition of CT to T does significantly improve the RFS chance even in ER positive tumours.[8] Thus it is plausible to assume that the early advantage of replacing T with an AI, which should be theoretically related to the increased chance of controlling primarily T resistant clones, might be flawed in the patients candidate to receive adjuvant CT as well. The most recent analysis of ATAC data relative to time to recurrence according to assigned treatment appears to confirm that in patients previously treated with CT the benefit achieved by anastrozole was lower than the benefit achieved in the patients treated with T alone and the difference anylonger statistically significant.[3]

Another, may be more important, argument against the use of upfront treatment with AI is the lack of any convincing effect of such an approach on breast cancer and overall mortality,in spite of the fact that both ATAC and BIG 1–98 trials are large and data quite mature.[3,9] No effect on mortality comes also from the metanalysis of the two trials, which includes more than 9.000 patients.[10] As cure still remains the major goal of adjuvant treatment of breast cancer, it is questionable at this point wether replacing T with an AI since the beginning should really represent the gold standard for all women with endocrine-sensitive tumours, also in view of the side effects that so prolonged oestrogen-deprivation might exert on bone resorption or ischaemic disease and of the increased costs of treatment.[11] In fact, in contrast to previous findings, a small,but statistically significant, breast cancer- and overall mortality advantage comes out from two of the four trials on switching and from the different metanalysis available so far,including the most recent AIOG metanalysis which confirms the positive effect of switching on both breast-cancer and overall mortality.[10,12–15]

In the absence of any direct comparative data between upfront *versus* sequencing strategies, mathematical models, which are based on previous trials data, were developed to predict the relative merits of the different strategies,and although conclusions are, some-what ,contrasting all these models suggest that sequencing should be expected to achieve comparable,if not better,results as compared to the strategies based on the up-front use of AI.[16]

Treatment costs can represent another major issue which might refrain from using AI. Data about drug costs, taken from US published wholesale acquisition costs, showed that anastrozole costs US$6.56 per day whereas generic T US $1.33. The sequential regimen is promising in keeping treatment costs low, because, intuitively, giving an AI for 2–3 years is cheaper that giving it for 5 years.[17] Health economic studies confirmed that switching is a cost-effective and a cost-useful option.

While awaiting the upcoming results from the sequential arms of the BIG 1–98 trial and the data from the amended TEAM trial, there is no doubt that switching to AI is not only strongly advisable for patients already on treatment with T from 2 or 3 years,but might represent a reasonable initial choice for all women with endocrine

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sensitive tumours,unless it might be reasonably argued that they might be intolerant to or anyway unsuitable for receiving T.

References:

1. Paepke S, Jacobs VR, Ohlinger R, et al. Treatment strategies that effectively reduce early recurrence risk in postmenopausal women with endocrine-sensitive breast cancer: AIs upfront vs. switching. *J Cancer Res Clin Oncol* 2007;**133**:905–16.
2. Cui X, Schiff R, Arpino G, et al. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. *J Clin Oncol* 2005;**23**:7721–35.
3. Forbes JF, Cuzick J, Buzdar Aother participants of Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;**9**:45–53.
4. Viale G, Regan MM, Maiorano E, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1–98. *J Clin Oncol* 2007;**25**:3846–52.
5. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. *J Clin Oncol* 2008;**26**:1059–65.
6. Carlson RW, Brown E, Burstein HJ, et al. NCCN Task Force Report: Adjuvant Therapy for Breast Cancer. *J Natl Compr Canc Netw* 2006;**4 Suppl 1**:S1–S26.
7. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007;**18**:1133–44.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.
9. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. *J Clin Oncol* 2007;**25**:486–92.
10. Peto R, for the Early Breast Cancer Trialists' Collaborative Group.The worldwide overview: new results for systemic adjuvant therapies. San Antonio Breast Cancer Conference 2007- Plenary Lecture.
11. Perez EA. Safety of aromatase inhibitors in the adjuvant setting. *Breast Cancer Res Treat* 2007;**105 Suppl 1**:75–89.
12. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;**369**:559–70.
13. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. *J Clin Oncol* 2007;**25**:2664–70.
14. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006;**7**:991–6.
15. Boccardo F, Rubagotti A, Aldrighetti D, et al. Switching to an aromatase inhibitor provides mortality benefit in early breast carcinoma: pooled analysis of 2 consecutive trials. *Cancer* 2007;**109**:1060–7.
16. Punglia RS, Knuntz KM, Winer EP, et al. Optimizing adjuvant endocrine therapy in postmenopausal women with early stage breast cancer: a decision analysis. *J Clin Oncol* 2005;**23**:5178–87.
17. Locker GY, Mansel R, Cella D, et al. Cost-effectiveness analysis of anastrozole versus tamoxifen as primary adjuvant therapy for postmenopausal women with early breast cancer: a US healthcare system perspective. The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. *Breast Cancer Res Treat* 2007;**106**:229–38.

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IS ORAL METRONOMIC CYCLOPHOSPHAMIDE (CTX) AN EFFECTIVE PALLIATIVE TREATMENT FOR PATIENTS WITH METASTATIC BREAST CARCINOMA (ABC)? EXPERIENCE FROM A RETROSPECTIVE SERIES OF PATIENTS

H. Boussen [a], G. Bellavia [b], R. Agueli [b], V. Gebbia [b]. [a] *Medical Oncology, Institut Salah Azaiz, Tunis, Tunisia.* [b] *University of Palermo La Maddalena Cancer Clinic, Palermo, Italy*

Oral metronomic chemotherapy is a therapeutic option which is particularly attractive for its ease of administration and low toxic burden. Its mechanism of action probably involves an anti-angiogenetic effects rather a classical antiproliferative effect like standard maximally tolerated dose-based regimens. Patients and methods: A retrospective analysis of 22 pts with ABC was carried out with the aim of reporting activity in terms of response rate, tumour-related symptoms control, outcome and toxicity. All patients had hormonal therapy-resistant metastatic disease and had previously received two lines of chemotherapy. All patients were treated with oral CTX 50 mg/day without interruption until re-evaluation or progressive disease. Results: An objective response (1 complete and 2 partial responses) was seen in 14% of patients (95%CL 5–28%). Stable disease with a median duration of 5 months (range 3–7months) was recorded in 8 cases (36%; 95%CL 16–56%) for a TGCR of 50%. Symptoms control was achieved in 54% of cases. Toxicity was very mild and easily manageable. No cases of extra-haematological grade 3-toxicity were observed. Grade 3 non-febrile neutropenia were recorded in 9% of cases. Conclusions: Although retrospectively recorded data presented in this study support the use of an oral metronomic chemotherapy in patients with ABC. Relatively mild activity is however seen in heavily pretreated patients without significant side-effects. Further studies are warranted to optimise the treatment schedule and to select patients who may benefit from such an approach.

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