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REVIEW

Neoadjuvant endocrine treatment: Precious but insufficiently discovered issue

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ABSTRACT

We would like to emphazise the importance of neoadjuvant endocrine treatment which is overshadowed by neoadjuvant chemotherapy for breast cancer patients. Missing knowledge is evaluation in terms of conventional notion of neoadjuvant chemotherapy that is it better to complete before surgery at least for some selected patients? Another point is, since it is a long term treatment, may be it will be a way give patients the chance to follow up without surgery. So this correspondence tries to ask two questions; shall we think about lengthening the duration of neoadjuvant endocrine treatment in selected patients and who are these patients?

Keywords: breast cancer, neoadjuvant treatment, endocrine treatment.

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INTRODUCTION

The goals of neoadjuvant systemic therapy in breast cancer are to increase local control and downstage tumor size to allow breast-conserving surgery (BCS) or mastectomy when the tumor is initially inoperable, to increase survival via pathologic complete responses (pCR) and also to tailor treatments through the oppurtunity that neoadjuvant setting provides by identifing predictive factors and biomarkers. Data has shown that chemotherapy that is suitable for the patient should be completed before surgery just the same as adjuvant period .

Neoadjuvant endocrine treatment (NAET) has been regarded as an option for elderly medically inoperabl and fragile patient group till 2000s but later on data has shown that it is as effective as neoadjuvant chemotherapy in regards of clinical response and pCR rates and somewhat more effective in regards of BCS rates whereas being less toxic [1,2].

Important question is when and how to use NAET and to whom. For premenopausal patients it was shown that when compared to NAET, a significant benefit of chemotherapy was seen with response rates of 75% and 44% respectively (p: 0.027) in GEICAM/2006-03 study [1]. If NAET is to be used in a selected premenapousal patient, then the choice should be aromatase inhibitors and goserelin combination since overall responses were shown to be higher compared to tamoxifen and goserelin [3].

In postmenapousal patients, although overall survival datas are still immature, NAET especially aromatase inhibitors rather than tamoxifen, is more effective than chemotherapy both about clinical responses and BCS rates and it wasshoen that all three aromatase inhibitors have similar activity [4,5]. In the ALTERNATE trial which randomizes patients with cT2–4 N0-3 M0 ER+/Her2– invasive breast cancer to either anastrozole, fulvestrant or its combination to assess a biomarker-driven treatment strategy, endocrine sensitive disease rate that was described as pCR or PEPI-0 residual disease (Ki67 ≤ 2.7%) difference between the fulvestrant containing arms and the anastrazole arm was not > 10%, so didn't reach the significance boundary

[6]. So fulvestrant seems not to be an option yet. However this strategy incorporates the findings that higher expression of Ki67 after 2 weeks of NAET is associated with poor recurrence-free survival for NAET.

CDK 4/6 inhibitors, that have been cornerstones in the treatment of metastatic ER+/ HER2 – group, were shown to molecularly downstage tumors similar to chemotherapy and cause statistically significant reductions in Ki67 levels and better complete cell cycle arrest rates. But still PEPI 0 rates in the CDK4/6 combination arm were not different from aromatase inhibitor only arm [7,8]. The same is true for PIK3CA inhibitors. Overall response rates have increased significantly both in the intend to treat population and PIK3CA mutant group, but pCR rates didn't differ in between combination or aromatase inhibitor only arm [9].

Up to date strong ER positivity, low Ki67 levels achieved after 2 to 4 weeks of NAET (cut off may be <10%) and being postmenapousal seem the most reliable predcitive markers for NAET. Neoadjuvant endocrine trials have shown that longer NAET periods resulted in higher response rates but missing area in these trials is the evaluation in terms of the conventional notion of neoadjuvant chemotherapy that it is better to complete before surgery, at least for some selected patients who will probably gain most benefit from this treatment. Another point is that since it is a long term treatment (suggested duration of adjuvant endocrine treatment is in between 5- 10 years) may be it will be a way give some patients the chance to follow up without surgery. So shall we think about lengthening the duration of neoadjuvant endocrine treatment in selected patients and who are these selected patients? May be for selected postmenapousal, strong ER+ HER2 – breast cancer patient whose tumor has shown decreased Ki67 levels after 2-4 weeks of treatment or for any other selected patient group? Can this be an ultimate way of breast conserving and to eliminate breast surgery in these selected cases? While combination strategy trials are in progress, detected predictive markers for long term responders will be very precious in this era.

CONCLUSION

In conclusion, we would like to emphazise the importance of NAET, a treatment that is overshadowed by neoadjuvant chemotherapy for breast cancer patients. It is obvious that ongoing trials will enlighten us more about the dark sides of neoadjuvant endocrine teatment.

Author contribution

Study conception and design: AO, ÖA; draft manuscript preparation: AO, ÖA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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