HORMONAL TREATMENT IN EARLY BREAST CANCER-WHICH PATIENT,WHAT STRATEGY?

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Abstract: *Breast cancer hormonal treatment in our days is important because meta-analysis showed semnificative gain in recurence and breast cancer mortality. Sometimes is dificult to chose the strategy we want to use. AIS are now routinely recommended for postmenopausal woman with HR+ tumors, particulary for woman at higher risk of relapse.*

Cuvinte cheie: *cancer de san, inhibitori de aromataza, Tamoxifen*

Rezumat: *In zilele noastre tratamentul hormonal al cancerului de san este important intrucat meta-analizele au aratat un castig semnificativ in ceea ce priveste recidiva si mortalitatea prin cancer de san. Uneori este dificil sa alegem strategia pe care dorim sa o folosim.AIS sunt acum recomandati de rutina pentru femeia in postmenopauza cu tumori CR+ in particular pentru femeia cu risc inalt de recidiva.*

SCIENTIFICAL ARTICLE OF A THEORETICALLY PREDOMINANCE

Breast cancer statistics show that the majority of women diagnosed with breast cancer are postmenopausal.Most breast cancers in postmenopausal women are hormone receptor positive.(i.e.,ER+and/or PR+).Adjuvant therapy increases the chance for long-term survival.Hormone receptor positive(HR+) breast cancer typically have a long natural history. In women treated with tamoxifen x 5 years,over half of all recurrences occur in years 6-11,therefore the ideal treatment approach would be to impact both early and late recurrences.

EBCTCG Meta-Analysis shows that Tamoxifen improves DFS and OS in ER-Positive early breast cancer (15-year gain 11.8% in DFS and 15-year gain 9.2% in mortality).

But, there are limitations with Tamoxifen. Despite improvement in DFS and OS, significant risk of relapse and death remains. Majority of benefit is seen in the first 2 years of treatment with lower incremental gains thereafter, in time resistance to Tamoxifen can develop.Also,potentially serious side effects are associated with Tamoxifen such as thrombembolic events and endometrial cancer.

Based on Landmark Adjuvant AI trials, AIs are now routinely recommended for postmenopausal women with HR+ tumors:

- St Gallen Expert Panel Consensus 2009 - results from trials continue to support the benefit of AIs in postmenopausal women with HR+ breast cancer.Benefit may be particularly marked for women at higher risk of relapse.
- NCCN Guidelines: treatment options for postmenopausal women include 5 years of AI,2 to 3 years of Tamoxifen followed by AI to complete 5 years(or more) of endocrine therapy,or 4.5 to 6 years of Tamoxifen followed 5 years of an AI.
- ASCO technology assessment-adjuvant therapy for postmenopausal women with HR+ breast cancer should include an AI.

When there are several treatment options,how does one choose?Is one strategy superior to the rest concerning efficacy, toxity profile or improved quality of life? Is one strategy more suited to which patient?

We have to consider tumor characteristic or subtype, pacient characteristics and comorbidities and cost.

For a newly diagnosed patient,the question is which is the optimal strategy?

BIG 1-98 trial directly compares the different strategies and long-term outcomes continue to emerge.

TEAM is the first trial prospectively powered to test superiority of upfront AI compared to a specific sequential strategy.We cannot expect randomized clinical trials for every scenario in oncology.We have to use modeling yields valuable information and meta-analysis.

Prognostic and predictive biomarker models were studied in trials.In ATAC quantitative expression of ER/PR and HER-2 status did not identify patients with differential relative benefit from anastrozole over tamoxifen.

In BIG 1-98 composite prognostic profile of clinico-pathological data and biological markers was better able to predict the relative treatment benefit.

In TEAM multiple molecular and clinical factors impact on early risk of relapse (PR, quantitative HER2, nodal status, grade, tumor size and age). Using risk models of early relapse in exemestane responsive group may further aid the patient selection for initial or delayed treatment with AIs.

Meta-analysis of Randomized Trials of Monotherapy and Switching Strategies in breast cancer recurrence show that in Tamoxifen vs. Upfront AI 5-year gain 2.9% and 8 year gain 3.9%. Whereas in Tamoxifen vs.Switch 3 year gain 3.1% and 6 year gain 3.5%.Breast cancer mortality-Tamoxifen vs.Upfront AI 5-years gain 1.1% and 8-years gain 0.5%.Tamoxifen vs. Upfront AI time since treantments differ 3-year gain 0.7% and 6 year gain 1.6%.

At this time, clinical decisions are made based on patient characteristics and side effect profiles. Patient stratification: women at very low risk of recurrence choose the best tolerated agent, women at very high risk of recurrence need to be taken into consideration, women of uncertain menopausal

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status need effective and safe therapy.

Still, there are many remaining questions.How will the use of bisphosphonates be factored in bone health? What is the optimal duration of AI therapy after a switch from Tamoxifen? Should duration of AI be tailored to breast cancer recurrence? Should a low-risk patient who has completed 5 years of AI therapy receive an additional year of AI therapy? Should a high-risk patient, after a switch strategy, receive additional years of AI therapy? Are there meaningful differences in side effects profiles among the AIs?

Adjuvant AI trials concerning safety show that treatment with tamoxifen can produce: genitourinary bleeding, endometrial cancer and venous thromboembolism. Aromatase inhibitors can produce: osteoporosis, bone fracture, arthralgia/myalgia, sexual disfunction. Hot flashes/night sweats, headache/dizziness, GI side effects, compliance, are more or less the same for both.

Arthralgia and AI therapy ~20% and 36% of AI treated patients developed arthralgias and up to 20% discontinue for this reason.

Management of musculoskeletal symptoms from AI therapy

Physical examination and patient history that are required to rule out- other causes (e.g.,osteoarthritis, bone metastases) and for that imaging studies were appropriate: articular vs.non-articular, inflamatoryvs. non - inflamatory pain.

Pain management with a combination of: lifestyle changes (e.g.,exercise) and pharmacologic interventions (e.g., NSAIDs, glucosamine, topical medications 9e.g., capsaicin). AI drug holiday of 3-4 weeks is helpful in confirming AI as the cause of musculoskeletal symptoms.If symptoms significantly affect quality of life or impair activities of daily living,we should consider to switch to another endocrine agent.

Osteoporosis and AI therapy

Effects of AIs on bone should be considered in the context of theit superior efficacy, because bone loss is not life-threatening-osteoporotic therapy is highly effective and can be given with AIs.

Bone health an AI therapy

Bone loss should be a consideration in women on AI treatment. ATAC trial showed that, no women with normalBMD at baseline had developed osteoporosis at 5 years. BMD appeared to recover or slow down once the patients stopped treatment.Regular BMD monitoring is required on patients at risk for osteoporosis such as patients over 60 years, smoking, that have a family history of osteoporosis and a low body mass index. We should also discuss lifestyle changes that may improve/maintain bone health and, when necessary, bisphosphonate therapy can prevent further bone loss, so that patients can continue with AI therapy.

Cardiovascular health and AI therapy

No current evidence suggests that the AIs have a particular adverse effect on CV health. Differences in lipid levels may have more to do with the protective effect of Tamoxifen on lipid levels than with an adverse effect of the AI. Patients receiving endocrine treatment should undergo a CV risk assessment-blood pressure, cholesterol levels and similar parameters should be monitored as part of a routine health check.No specific management strategies are required but women are encouraged to exercise and quit smoking.

Key points from TEAM

Is the first trial prospectively powered to test superiority of 5 years of AI compared to a specific sequential strategy. TEAM did not show a difference in efficacy between 5 years of exemestane compared to the sequence TAM-EXE. HR: DFS=0.97, OS=1.00; NS p value for both.

For postmenopausal women with endocrine sensitive early breast cancer the use of either 5 years of upfront exemestane or TAM show that EXE are appropriate treatment options.Safety profile is consistent with known side effects of exemestane and tamoxifen.

Key points from IES

Switch to exemestane significantly improves efficacy and safety versus tamoxifen in the ER positive/unknown population: DFS: 18% risk reduction for absolute benefit of 3.9%; OS:14% risk reduction fo absolute benefit of 2.4%.

The 91-month mature exemestane IES results provide reliable evidence in the switch setting. Efficacy benefits across patient subsets are commonly seen in clinical practice.

Furthermore, switching to exemestane does not compromise safety or QoL because exemestane is generally safe and well-tolerated, serious side effects are rare and the clinical benefits of exemestane were achieved without any detrimental effect on QoL.

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