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Rationale for an ISTH SCC guidance document on:
Use of hormonal therapy in high thrombotic risk cancer populations

Participating SSCs
Hemostasis & Malignancy (Zwicker)
Women's Health Issues in Thrombosis and Hemostasis (Othman)
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Statement of Purpose
Breast cancer in itself is a low thrombotic risk cancer, but chemotherapy and hormonal therapy increase the risk of thrombosis (1). The two main groups of hormonal therapies used to treat breast cancer are tamoxifen (a selective estrogen receptor modulator, SERM) and aromatase inhibitors (AI). These agents may be used as adjuvant therapy for periods of years and have been shown to increase survival, or as therapy in the metastatic setting. Tamoxifen and AIs are both associated with an increased risk of thrombosis, but the thrombotic risk profile appears to differ between these drugs (1–3).

Tamoxifen is associated with a 2 to 4-fold increase in the risk of venous thromboembolism (VTE), corresponding to an annual incidence of at least 2% (1). The relative risk is highest in the 3 months after initiation of tamoxifen (1), but persists over time (4). The tamoxifen-associated VTE risk is even higher in patients with additional VTE risk factors, such as factor V Leiden mutation (5). On the other hand, tamoxifen is not associated with an increased risk of arterial thrombosis (i.e., myocardial infarction or stroke), and a meta-analysis of randomized controlled trials even demonstrated a reduction in adverse arterial cardiovascular events compared to placebo (3, 6).

A population-based cohort study did not show an increase in VTE with AIs, compared to no AI therapy (1). Compared to tamoxifen, AIs were associated with an increased risk of cardiovascular mortality in a recent historical cohort study, with the curves separating after two years of therapy. The risk of ischemic stroke and myocardial infarction was numerically increased in this study, but not statistically significant (2). Whether this is due to a cardioprotective effect of tamoxifen or adverse effects of AIs remains to be determined (3).

There is little evidence on the thrombotic risk of additional hormonal therapy agents such as Fulvestrant (a selective estrogen receptor degrader, SERD), while there is emerging data suggesting an increased risk of VTE in breast cancer patients treated with Cyclin-dependent Kinase Inhibitors, such as Palbociclib (7).

These thrombotic risks raise important clinical questions when selecting the hormonal therapies in patients with an increased risk for or history of thrombosis. There are currently no guidance documents on management of the thrombotic risk in cancer patients receiving hormonal therapy in cancer.

Content Outline

a) Drug-drug interactions in breast and prostate cancer and antithrombotics
b) Hormonal therapy in breast cancer patients with a high risk for or history of VTE.
    i. Assessing the thrombotic risk
    ii. Selecting the optimal hormonal therapy from a thrombotic standpoint
    iii. In the presence of prohibitive thrombotic risk and absence of therapeutic alternatives, should prophylactic antithrombotic therapy be considered to enable hormonal therapy?
c) Hormonal therapy in breast cancer patients with a high risk for or history of arterial thrombosis (see a.i-iii)
d) Managing hormonal therapy in cancer patients with acute VTE or acute arterial thrombosis.

e) Oral contraceptive pills (OCP) and hormone replacement therapy (HRT) in patients with cancer at increased risk for VTE.
f) Thrombotic risk (venous and arterial) associated with hormone therapy in males with prostate cancer

Expected Timeline:

- October/Nov – literature review
- December – meeting to discuss guidance statements
- January – Manuscript draft
- July 2022 – Presentation at ISTH

Expected Outcomes:

SSC Guidance Publication in JTH

References

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