Appendix 4. Prevention of thromboembolism events during chemotherapy

Thromboembolic events (TEE) occur more frequently in patients with germ cell tumours (GCT) receiving chemotherapy than in young males under chemotherapy for other cancers [1]. A large study, comparing TEE incidence between GCT patients and men without GCT found GCT patients undergoing BEP [Bleomycin, etoposide, cisplatin] chemotherapy had more TEE within the first year: with hazard ratios (HRs) of 6.3, 6.0, and 24.7 for myocardial infarction, cerebrovascular accident, and venous thromboembolism, respectively [2].

Recent randomised controlled trials (RCTs) have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and report a relative risk reduction of 30-60% in venous thromboembolic events (VTE) but a doubling of bleeding risk [3-6]. Based on these results, the American Society of Clinical Oncology Clinical Practice Guideline Update recommended thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) to cancer patients with a high risk of VTE and low risk of bleeding [7]. Metastatic germ cell tumour (mGCT) patients were under-represented in these trials and so it is not clear whether this recommendation applies to this group although retrospective data suggested a similar efficacy of VTE prophylaxis [8, 9].

Several retrospective cohort studies published mGCT specific VTE and bleeding risks as well as potential risk factors for VTE. In the largest multi-centre cohort study a cumulative VTE incidence of 11% and < 1% VTEs was observed [10]. Nearly all VTEs occurred shortly prior to, or during, the first 90 days of commencing cisplatin chemotherapy. A cumulative VTE incidence of 5% during or after chemotherapy occurred in men without any risk factors for VTE. Even with thromboprophylaxis the rate of VTE was high. Bleeding was observed in 0.5-1.1% of men not on thromboprophylaxis versus 2.5-14.5% of men receiving thromboprophylaxis.

The EAU Guideline panel has discussed a recommendation regarding thromboprophylaxis in mGCT. All members agreed that men with mGCTs undergoing chemotherapy are at high-risk for VTE and low risk of bleeding. The VTE outcome definitions are heterogeneous and, in most of the studies, only univariable analyses without external validation were performed. Given the apparent high VTE incidence and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men versus those who restricted thromboprophylaxis to men with certain risk factors. For the final guideline recommendation, the panel agreed that based on the current literature only a generic statement about the use of thromboprophylaxis should be given until stronger evidence is available. Therefore, RCTs or well conducted prospective cohort studies with an adequate sample size allowing adjusting for potential confounders and numerous risk factors are needed to clarify the indication for and optimal duration of thromboprophylaxis.

However, no RCTs are underway to answer those questions and the only two retrospective studies analysed the risk benefits of thromboprophylaxis reported contradictory results [11, 12]. Both studies were hampered by a limited number of men with VTE, thus limiting the ability to account for known confounders which limited the conclusion from both studies. A generic statement in the TC Guideline should remind clinicians about the high risk of VTE and to prescribe thromboprophylaxis after balancing the risk and benefits. Additionally, the majority of the panel agreed that a central venous-access device should be avoided whenever possible as this represents the only modifiable risk factor, which remained significantly associated with VTE in a multivariable risk-prediction model [10].

If thromboprophylaxis is chosen either low molecular weight heparin (LMWH) or oral thromboprophylaxis (apixaban 2.5 mg bid or rivaroxaban 10 mg qd) should be used and should be started before chemotherapy and continued for at least 90 days. Thromboprophylaxis should only be prescribed if no drug interactions or significant risk factors for bleeding are present. Although GCT patients specific risk factors for bleeding are ill-defined the personal experience of panel members

and case reports suggest that men with organ infiltration, cerebral metastases and/or significantly elevated β-hCG levels suggestive of choriocarcinoma are at a higher risk of bleeding.

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