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Original Research

Predicting and preventing thromboembolic events in patients receiving cisplatin-based chemotherapy for germ cell tumours

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Abstract ***Background:*** Patients with germ cell tumours (GCT) receiving cisplatin-based chemotherapy are at high risk of thromboembolic events (TEE). Previously, we identified serum lactate dehydrogenase (LDH) and body surface area (BSA) as independent predictive factors for TEE.

The aim of this study was to validate these predictive factors and to assess the impact of thromboembolism prophylaxis in patients at risk of deep venous thrombosis (DVT).

Methods: Between 2001 and 2014, 295 patients received first-line cisplatin-based chemotherapy for GCT. Preventive anticoagulation with low-molecular-weight heparin (LMWH) was progressively implemented in patients with predictive factors. Sixteen patients with evidence of TEE before starting chemotherapy were excluded from the analysis.

Results: Among 279 eligible patients, a TEE occurred in 38 (14%) consisting of DVT (n = 26), arterial thrombosis (n = 2), and superficial thrombophlebitis (n = 10). DVT occurred in 26 (12.7%) of 204 patients with risk factors versus two (2.6%) of 75 patients with no risk factors (p = 0.01).

After a prevention protocol was progressively implemented from 2005, primary thromboprophylaxis was administered to 104 patients (68%) with risk factors. Among patients at risk (n = 151), the incidence of DVT decreased by roughly half when they received a LMWH: 9/97 (9.2%) and 9/54 (16.6%), respectively (p = 0.23).

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Conclusion: Patients with GCT who receive cisplatin-based chemotherapy are at risk of developing a TEE which can be predicted by elevated serum LDH. To our knowledge this is the first study exploring LMWH as thromboprophylaxis in GCT patients. A prospective trial testing prophylactic anticoagulation is warranted.

1. Introduction

Germ cell tumours (GCT) are the most common cancers in young men and, despite metastatic spreading, are highly curable with cisplatin-based chemotherapy followed by surgical resection of residual masses [1].

While most patients can be cured [2,3], treatment-related toxicities including haematologic, pulmonary fibrosis, neuropathy, Raynaud's phenomenon, metabolic syndrome, renal dysfunction, peripheral neuropathy, infertility, hypercholesterolaemia and increased cardiovascular risk, remain problematic [4–6]. Reducing the morbidity and the acute and long-term toxicities of treatment requires greater focus.

In past years, various groups have reported higher incidences of acute thromboembolic events (TEE) in patients with GCT treated with cisplatin-based chemotherapy [7–10]. The occurrence of acute TEE in young patients can be life threatening and lead to long-term complications. The role of chemotherapy in cardiovascular toxicity is still controversial [11].

We previously demonstrated that patients with GCT who receive cisplatin-based chemotherapy have a higher risk of TEE compared to other cancer patients of the same age who receive cisplatin-based chemotherapy (19% versus 6%; relative risk [RR]: 3.4; $p < 0.01$) [7]. Elevated serum lactate dehydrogenase (LDH) and a high body surface area (BSA) were identified as independent prognostic factors for TEE: the incidence of TEE was 26% (95% confidence interval (CI): 17–37) and 4% (95% CI: 1–19) in patients with and without these risk factors, respectively [7]. Based on these data, from the mid-2000s, we introduced routine preventive anticoagulation with low-molecular-weight heparin (LMWH) in GCT patients with these risk factors.

The main objective of this study was to assess the impact of a thromboprophylaxis policy in patients with GCT at risk of deep venous thrombosis (DVT). Secondary objectives included the exploration of risk factors for TEE, and the validation of elevated LDH and high BSA as risk factors.

2. Materials and methods

2.1. Sample design

Using a computerised database and a systematic chart review, we identified all patients with GCT treated at Gustave Roussy, Villejuif, France, between January 2001 and June 2014. This retrospective study included 279 male patients older than 16 years with pathological evidence of a GCT (pure seminoma or non seminoma), and a testicular or an extragonadal primary site, who received first-line chemotherapy. Patients previously treated with chemotherapy or radiotherapy were excluded, as were those with a TEE diagnosed before the initiation of chemotherapy.

Pre-treatment evaluation consisted of a complete physical examination, blood chemistry (blood urea nitrogen, creatinine, creatinine clearance, electrolytes, magnesium, hepatic enzymes), a complete blood count, serum lactic dehydrogenase (LDH), and radioimmunological determination of serum human chorionic gonadotropin (hCG) and alpha fetoprotein (AFP) levels. A computed tomography (CT) scan of the pelvis, abdomen, and chest was also performed, as was brain imaging in the event of supra-diaphragmatic lymph nodes and/or visceral metastases.

A TEE was defined as the occurrence of a deep or superficial venous thrombosis, or any arterial thromboembolic complication, from the first day of chemotherapy to 6 months after the last cycle of chemotherapy due to the long storage of cisplatin [12,13]. Radiologic evidence was obtained by Doppler ultrasonography or CT scan. The evolution of TEE was documented in terms of complications, relapse and long-term functional complications.

From 2005, prophylactic anticoagulation with LMWH was recommended and progressively implemented in patients with elevated LDH and/or a BSA >1.9 before the initiation of chemotherapy. All patients had GCT and were divided into two cohorts: 75 patients treated between January 2001 and December 2004 (cohort 1), and 204 patients treated between January 2005 and June 2014 (cohort 2).

All patients received first-line cisplatin-based chemotherapy at a dose of 100 mg/m^2. Cisplatin was mainly combined with bleomycin and etoposide (BEP and EP regimens), but some patients received paclitaxel-BEP per the European Organisation for Research and Treatment of Cancer 30983 trial [14], or the Groupe d'étude des tumeurs urogénitales (GETUG) 13 dose dense regimen [15]. Treatment was given with adjuvant intent in clinical stage I patients (n = 47, 17%), or as first-line therapy for advanced disease (n = 232, 83%).