What is the optimum strategy for thromboembolic prophylaxis following extrapleural pneumonectomy in patients with malignant pleural mesothelioma?†

Andrea Billè, Lawrence Okiror, Wolfram Karenovics, John Pilling and Loïc Lang-Lazdunski*

Department of Thoracic Surgery, Guy’s & St Thomas’ Hospital NHS Foundation Trust and Division of Cancer Studies, King’s College London, London, UK

* Corresponding author. Department of Thoracic Surgery, 6th Floor Borough Wing, Guy’s Hospital, London SE1 9RT, UK. Tel: +44-207-1881038; fax: +44-207-1881016; e-mail: loic.lang-lazdunski@gstt.nhs.uk (L. Lang-Lazdunski).

Received 7 January 2012; received in revised form 28 February 2012; accepted 23 March 2012

Abstract

Malignant pleural mesothelioma (MPM) increases the risk of venous thromboembolic (VTE) events. This risk is higher following extrapleural pneumonectomy (EPP) as part of trimodality therapy, where VTE can be catastrophic. In our series, the impact of warfarin in preventing a pulmonary embolus (PE) after neoadjuvant chemotherapy and EPP for MPM was analysed. A retrospective analysis of 21 consecutive patients undergoing EPP for MPM was conducted. The first 10 patients (Group A) had VTE prophylaxis by subcutaneous enoxaparin and compression stockings commenced a day prior to surgery, intraoperative pneumatic calf compression and early postoperative mobilization. Enoxaparin was continued for 30 days postoperatively. The following 11 patients (Group B) had the same VTE prophylaxis, together with warfarin, started prior to hospital discharge and continued for 6 months postoperatively. All patients had a computed tomography pulmonary angiogram within 8 weeks after surgery and a full examination at 1, 3, 6 and 12 months. Both groups were comparable for characteristics. Three patients in Group A suffered a PE at 4, 6 and 16 weeks postoperatively. One PE was fatal. No patient in Group B suffered VTE (P = 0.05, χ² test) or haemorrhagic complications. Warfarin anticoagulation following EPP is feasible and safe, and is associated with a significant reduction in VTE complications.

Keywords: Malignant pleural mesothelioma · Extrapleural pneumonectomy · Pulmonary embolism · Anticoagulation

INTRODUCTION

Venous thromboembolism (VTE) is a particularly common problem in cancer patients [1]. The incidence of thromboembolic events in patients with malignant pleural mesothelioma (MPM) has been reported to be as high as 27% [2]. In patients undergoing extrapleural pneumonectomy (EPP) as part of trimodality therapy, the occurrence of VTE, especially pulmonary embolism, is potentially catastrophic. The role of heparins and low-molecular-weight heparins (LMWHs) compared with oral anticoagulation for the prevention of VTE in cancer patients have been extensively studied [3, 4]. The studies have demonstrated a survival benefit with LMWHs for VTE prophylaxis, possibly related to an antineoplastic effect [5]. LMWHs are routinely used for thromboprophylaxis in patients undergoing lung resection for thoracic malignancy [6]. The role of long-term anticoagulation with vitamin K antagonists is less well established. The purpose of our study was to retrospectively evaluate the role of postoperative warfarin therapy in long-term anticoagulation in patients undergoing EPP as part of the trimodality therapy for MPM.

This is a retrospective review of a consecutive series of patients who underwent EPP for MPM over a 4-year period in a single thoracic surgical practice between April 2004 and May 2008.

All patients had a video assisted thoracic surgery procedure and a cervical mediastinoscopy prior to starting chemotherapy to confirm tissue diagnosis and rule out N2–N3 disease. Only patients with epithelioid and biphasic subtypes of mesothelioma and cT1–3N0–1M0 were considered for EPP.

Neoadjuvant chemotherapy consisted of three cycles of a combination of cisplatin (80 mg/m²) and gemcitabine (1000 mg/m²) before 2007 or a combination of cisplatin (80 mg/m²) and pemetrexed (500 mg/m²) after that date. Folic acid and vitamin B12 supplementation were given according to the local guidelines.

All patients had an echocardiogram to rule out a significant valvulopathy and to assess left and right ventricular functions. All patients had full lung function and cardiopulmonary exercise tests and measurement of VO₂max.

Preoperative staging was performed using an integrated computed-assisted tomography (CT) and positron emission tomography (18-FDG-PET-CT). The TNM staging system proposed by

1Presented at the 19th European Conference on General Thoracic Surgery, Marseille, France, 5–8 June 2011.
An EPP was performed through a large posterolateral thoracotomy (5th and 8th interspace). The pericardium was replaced with a polyglactin mesh (Vicryl, Ethicon, Johnson & Johnson Intl, St Stevens Woluwe, Belgium), and the diaphragm was replaced with a Gore Tex mesh (Dualmesh®, WL Gore & Associates, Flagstaff, AZ, USA) in all patients. The anterior mediastinal fat was resected en bloc with the specimen in all cases. The systematic dissection of the mediastinal and internal mammary lymph nodes was also performed to aid in the final pathological staging.

Patients were routinely referred for adjuvant radiotherapy, 6–8 weeks postoperatively. The prescribed dose was 54 Gy in 30 fractions over 6 weeks to the 100% isodose. For right-sided patients, it was not always possible to safely prescribe 54 Gy to the lower half of the field due to dose constraints to the liver. The minimum prescribed dose to the lower portion of the right-sided volumes was 45 Gy. A computed tomography (CT) scan from mid-neck to the iliac crests was acquired for target definition, delineation of normal tissue structures and radiotherapy dosimetry planning. The clinical target volume comprised the entire ipsilateral thoracic cavity from lung apex to the insertion of the diaphragm, the ipsilateral mediastinal pleura, the mediastinal tissues at sites where an evidence of tumour invasion was present, the ipsilateral mediastinum if node positive and the ipsilateral pericardial surface and full thickness of the thorax at the sites of surgical incision.

Radiotherapy was administered using a 6-MV linear accelerator and a three-dimensional, conformal technique with multi-leaf collimation. All patients had a VTE prophylaxis with enoxaparin 40 mg subcutaneously and thromboembolic deterrent stockings starting a day before surgery, intraoperative calf pneumatic compression and early postoperative mobilization. Enoxaparin was continued for 30 days after surgery. There were two groups of patients. In the first group (Group A, n = 10), VTE prophylaxis was as described above. In the second group (Group B, n = 11), in addition to the above-described VTE prophylaxis strategy, anticoagulation with warfarin, was started in-hospital before discharge and continued until 6 months postoperatively. Warfarin was administered to maintain a target international normalized ratio (INR) of 2.0–2.5. Enoxaparin was discontinued when INR was >2.0.

Following discharge, patients were reviewed at 4 weeks. All patients had a helical CT pulmonary angiogram within 8 weeks postoperatively. The CT scans were reviewed by a thoracic radiologist. Patients on warfarin were screened for clinically significant haemorrhagic events at clinical visits and by their family physicians. The details of thromboembolic events were obtained from the hospital and family physician records. All patients with VTE had the diagnosis confirmed by imaging (CT pulmonary angiogram [CTPA] for pulmonary embolism and duplex ultrasonography for leg deep vein thrombosis). Patients were subsequently followed up at 6 weeks, then 3, 6 and 12 months postoperatively.

Statistical methods
Continuous data are reported with medians and ranges, while categorical data are reported with counts and percentages. Patient characteristics were matched in the two groups. The survival curves were computed according to the Kaplan–Meier method and comparison between the groups of patients was performed using the log-rank test. Probability values <0.05 were considered statistically significant. All analyses were conducted using the SPSS 18 (SPSS Inc., Chicago, IL, USA) software package.

RESULTS
A total of 25 consecutive patients were considered for EPP between April 2004 and May 2008. Three underwent an exploratory thoracotomy only due to advanced-stage disease (T4) and one died of haemorrhage intraoperatively. Thus, 21 consecutive patients were entered into the study. The median age of all patients was 62 (range 52–68 years) and 19 patients (90%) were male. There was no 30-day mortality among operative survivors, but one patient died of septicemia at 2 months. Baseline characteristics were comparable with the two groups (Table 1). The median hospital length of stay was 14 days (range 10–71). Complications are listed in Table 2. All patients in Group B received warfarin and achieved a target INR of 2.0–2.5. All 21 patients had a helical CTPA within 8 weeks postoperatively. The median follow-up was 12 months. At the follow-up, three patients in Group A suffered a pulmonary embolus (PE) at 4 weeks, 6 weeks and 4 months postoperatively. One PE was fatal.

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of patients in both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Table 2: In-hospital postoperative complications after EPP (n = 21)</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>ARDS</td>
</tr>
<tr>
<td>Vocal cord palsy</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
</tr>
<tr>
<td>Late septicemia</td>
</tr>
<tr>
<td>PE</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Re-operation for bleeding</td>
</tr>
<tr>
<td>Bronchopleural fistula/empyema</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>
No patients in Group B had any VTE events (P = 0.05). No patients in either group suffered any clinically significant haemorrhagic events. One patient in Group B had an INR reaching a value of 6.0 during adjuvant radiotherapy following right EPP, but suffered no haemorrhagic complication. The dose of warfarin was adjusted to reach a target INR of >2.0–2.5.

**DISCUSSION**

The treatment of MPM often involves a multi-modality approach including surgery, chemotherapy and radiotherapy in carefully selected patients [8, 9]. The aim of surgery in MPM is to achieve the local control of the disease with a complete macroscopic resection (R0–R1). EPP usually involves en bloc resection of lung, pleura, pericardium and diaphragm, thereby removing all gross disease. The extensive nature of the resection is associated with significant morbidity and mortality and EPP is now controversial [10, 11]. Patients who have had EPP are at the risk of VTE because of the hypercoagulability state induced by the underlying cancer, the extensive surgery, long in-hospital stay and neoadjuvant chemotherapy. A pulmonary embolism in these patients is often catastrophic and carries a high mortality. In fact, DVT and PE have been consistently reported as complications of EPP with a severity grade of three or more in patients who have had preoperative induction chemotherapy [9] and this risk can persist for 6–9 months after surgery. In a large series, Sugarbaker et al. reported PE and DVT rates of 1.5 and 6.4%, respectively after EPP [12]. In patients having pneumonectomy for non-small cell lung cancer after neoadjuvant chemotherapy, the lethality of PE is similarly high. In a series of 176 pneumonectomies for primary lung cancer post-induction chemotherapy, Weder et al. [13] reported a mortality rate of 3%, half of which was due to PE. Similarly, Doddoli et al. [14] reported a 4% rate of VTE complications after pneumonectomy following induction chemotherapy. However, 14% of their patients died suddenly within 3 months of surgery and this author postulated that death could have been caused by an acute pulmonary embolism. This group routinely recommends long-term anticoagulation with vitamin K antagonists after pneumonectomy. In a large series of 1735 lung resections, Kalweit et al. [15] reported 19 cases of central pulmonary artery embolism in 20 patients undergoing autopsy, emphasizing the high lethality of pulmonary embolism after lung resection.

We postulated that continuing anticoagulation with warfarin for 6 months after surgery would reduce the risk of VTE significantly, without increasing the risk of haemorrhagic events. This strategy led to no episodes of pulmonary embolism in patients on warfarin for 6 months. Instead, in the no warfarin group, three patients developed a VTE event, one of which occurred while the patient was receiving radiotherapy. Of course, one concern with prolonged anticoagulation is an increased risk of bleeding, which could be fatal. This can happen particularly in patients after right EPP when liver irradiation can result in major coagulation disturbances. We had no haemorrhagic complications in all our patients on warfarin and all patients were able to achieve and maintain a target INR range of 2.0–2.5. We had to reduce the warfarin dose in two patients during radiotherapy when INR was increasing rapidly (>4). Thus, we recommend that INR is monitored regularly (twice weekly) during adjuvant radiotherapy after right EPP.

Our small series showed that prolonged anticoagulation with warfarin for 6 months after EPP may reduce the risk of VTE, with no significant risk of bleeding. A potential bias is obvious in that this is a small retrospective study with a limited number of patients. Hence, drawing conclusions and making recommendations may not be appropriate. Nevertheless, we believe that extending anticoagulation for 6 months after EPP may potentially prevent a catastrophic pulmonary embolism and is safe and easy to manage.

**Conflict of interest:** none declared.

**REFERENCES**