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Thromboembolism in lung cancer – An area of urgent unmet need

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ABSTRACT

Introduction: Thromboembolism is common in lung cancer. Current thromboprophylaxis guidelines lack specific recommendations for appropriate strategies in this high thrombotic risk patient cohort. We profiled lung cancer patients receiving anti-cancer therapy. Thromboembolism incidence and thromboembolism-related mortality rates are reported and we explored patient, disease, and treatment-related risk factors associated with higher thrombotic rates.
Methods: Retrospective review of lung cancer patients referred to a Comprehensive Cancer Centre between 01/07/2011 and 30/06/2012 for anti-cancer therapy. Data were collected from medical, pharmacy, pathology and diagnostic imaging electronic records.
Results: After a median follow up of 10 months (range: 0.03–32 months), 24/222 patients (10.8%) had developed radiologically confirmed thromboembolism; 131 events per 1000 person-years (95%CI 87–195). Thromboembolism occurred equally in patients with non-small cell and small cell lung cancer (10.8% and 10.5% respectively), and more frequently among patients with adenocarcinoma compared to squamous cell carcinoma (14.7% and 5.3% respectively). Chemotherapy-treated patients experienced thromboembolism more often than patients who did not receive chemotherapy (HR 5.7 95%CI 2.2–14.8). Radiotherapy was also associated with more frequent thromboembolism (HR 5.2 95%CI 2.0–13.2). New lung cancer diagnosis, presence of metastatic disease, second primary malignancy and Charlson Index ≥5 were also associated with higher rates of thromboembolism. Importantly, pharmacological thromboprophylaxis (P-TP) was not routinely or systematically prescribed for ambulant lung cancer patients during any treatment phase, at this institution. The majority (83%) of thromboembolic events occurred in the ambulatory care setting.
Conclusion: Morbidity and mortality from thromboembolism occurs frequently in lung cancer. Thromboprophylaxis guidelines should be developed for the ambulatory care setting.

1. Introduction

Lung cancer (LC) is the most common cause of cancer mortality in many countries, including Australia. Thromboembolism (TE) is reported in up to 14% of LC patients, a 20-fold increased risk in comparison to the general population and among the highest incidences of all cancer populations [1–3].

Cancer-associated thrombosis has substantial adverse health and economic consequences [4,5]. It is a potent negative predictor of survival and a leading cause of death [1,6]. Appropriate pharmacological thromboprophylaxis (P-TP) can be a highly cost-effective preventative strategy with the potential to reduce the incidence of TE in high-risk patients by up to 80% [7–9]. While all patients with cancer should be considered at risk of TE, the risk is dynamic, and the absolute magnitude and duration of TE risk is not equal for all patients or for a given individual over time. This heterogeneity in both TE and bleeding risk is further exaggerated during the cancer

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disease course and different intervention phases – emphasising the importance of a personalised risk-stratified approach rather than a broad application of P-TP in patients with cancer.

There is substantial variation in the TE incidence reported among LC patients (2–14%), which likely reflects this dynamic risk profile [1–3,5,10–16]. Reported rates likely underestimate the true incidence as registry data cannot adequately capture outpatient management, the arena in which the majority of LC patients are treated. Chemotherapy is one of the most important treatment-related factors in the aetiology of cancer associated TE, with most events occurring in the ambulatory care setting [16–20]. Subgroup analysis of LC patients within several large scale randomised studies of cancer patients undergoing chemotherapy demonstrated both safety and efficacy of P-TP in this setting [21–23]. The overall post-surgical TE incidence in LC (10.1%) is higher than the overall incidence rate among all cancers, and second only to gastrointestinal cancers [24]. All major international guidelines recommend P-TP in this setting; however the duration of therapy remains contentious [25–30]. Recent studies have demonstrated an extended period of TE risk for cancer patients, particularly following major surgery, beyond the standard 7–10 days of recommended P-TP [31]. Despite LC being the second most common cause of cancer associated TE in the post-surgical setting there is a lack of data defining the optimal duration of P-TP [25–30].

This retrospective cohort study reports the incidence and timing of TE across different stages of treatment (surgery, radiotherapy, chemotherapy and biologic agents) for a subset of LC patients treated at a dedicated cancer centre over a 12 month period.

2. Methods

2.1. Patient population

All LC patents referred to the Peter MacCallum Cancer Centre (Peter Mac) lung unit during the period 01/07/12–30/06/13 were screened for inclusion. Eligible patients had a diagnosis of small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), any disease stage (stage I–IV), and any disease status (newly diagnosed or pre-treated). Patients with a non-LC diagnosis and patients not receiving treatment primarily at Peter Mac (i.e. referred for opinion or staging only) were excluded.

2.2. Study design

A retrospective review of all patient records over the stated time frame was performed. Peter MacCallum Cancer Centre Ethics Committee (12/176) and Monash University Human Research Ethics Committee (CF13/1249 – 2013000624) approvals were obtained. The study was conducted according to the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research and the World Medical Association Declaration of Helsinki 2008 [32,33]. No funding was obtained.

Data collection included patient demographics (age, gender, eastern cooperative oncology group ECOG performance status), disease related information (diagnosis, histology, stage, (brain) metastasis), anticancer treatments (chemotherapy, chemo-radiotherapy, radiotherapy, surgery, biologic agents), and comorbidity and TE risk profiles. The Charlson Index [34] was utilised to evaluate the effect of commodities, with evaluation cut-off score of 5 based on recently published data in a similar patient cohort [15]. Individual comorbidities from the Charlson Index as well as other TE risk factors (obesity, history of prior TE and prior/current second primary malignancy) were collected.

The primary outcome measure was the incidence of radiologically confirmed symptomatic or clinically unsuspected TE. TE was defined as any pulmonary embolism (PE), deep vein thrombosis (DVT), venous thromboembolism (VTE) or arterial thromboembolism (ATE) as confirmed by radiologic imaging, computed tomography pulmonary angiogram (CTPA) or lower limb ultrasound. Fatal TE was defined as any death attributable to and within 6 weeks of a documented TE, or any death with medical documentation specifying TE event and probable contributory cause.

2.3. Data analysis

TE incidence rates are presented in terms of person-time (years). Individual subject follow-up (person-years at risk) was counted from date of first referral until the date of the first occurring event: TE, death, loss to follow-up (no medical records) or audit date. Subjects who did not experience the event of interest (TE) were treated in survival analyses as censored at end of follow-up. Subgroup analysis for the cumulative incidence of TE in patients with NSCLC vs. SCLC and adenocarcinoma vs. squamous cell carcinoma was conducted using log-rank tests. Median and range (continuous variables) and frequency and percentage (categorical variables), were used to describe patient, disease and treatment characteristics. Cox proportional hazards, PH, regression was used to analyse the association between treatment and TE (adjusting for age and sex). Variables exhibiting some evidence of univariate association with TE, i.e. with $p < 0.10$, were also adjusted for (metastatic disease, brain metastasis, second primary malignancy, new diagnosis and Charlson Index ≥ 5). To avoid over-fitting, models were restricted to a small number of covariates in recognition of the relatively small number of TE events [35]. Separate Cox PH models were constructed using time-varying and time-fixed treatment factors. In time-fixed analysis, treatment was considered a fixed event with no consideration for time of commencement, or duration, of therapy. The integrity of the PH assumption in the time-fixed models was tested by using a log-log plot of survival and Schoenfeld residuals [36]. In time-varying models both the duration of therapy and extended pro-thrombic state following therapy, were considered. Patients were assumed to be at a baseline thrombotic risk level until the day of commencing treatment whereupon they were assumed to be at elevated risk until the end of their pro-thrombotic state. The pro-thrombic effect of any treatment modality was defined as the duration of therapy plus 90 days. This is a similar approach to previously published models [3] and assumes that 90 days beyond treatment subjects will return to their baseline thrombotic risk level.

3. Results

3.1. Patients and treatment

804 patients were referred to the Peter Mac lung unit during the study period; 222 were eligible for inclusion (Fig. 1). The median period of follow-up from first hospital registration was 10.0 months (range: 0.03–32 months). Patients were followed for a total of 183.4 person-years. Patient characteristics are summarised in Table 1 with the majority being newly diagnosed disease (>75%), and with advanced disease (stage III–IV NSCLC, extensive disease SCLC) (>70%), NSCLC (>90%) and adenocarcinoma histological subtype (57%). Patients underwent a variety of treatments with near a third (61/222) receiving multiple lines of therapy, within the study period. Just under half of all patients received some form of chemotherapy, with the majority incorporating a platinum agent and as a combination chemo-radiotherapy. 73% (161/222) of patients received radiotherapy (alone or as combination chemo-radiotherapy), 19% (43/222) received therapy with a biologic agent and 19% (42/222) underwent surgical intervention. P-TP was not