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Research paper

The burden of neutropenic sepsis in patients with advanced non-small cell lung cancer treated with single-agent docetaxel: A retrospective study

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ABSTRACT

Objectives: To describe rates of confirmed and suspected neutropenic sepsis (NS) and associated hospital resource utilisation in patients with non-small cell lung cancer (NSCLC) treated with docetaxel monotherapy following relapse after ≥1 line of chemotherapy in routine UK clinical practice.

Materials and methods: A multi-centre, retrospective, observational research study was conducted in seven centres across England and Wales. Adult patients with stage III/IV NSCLC initiated on docetaxel monotherapy between 2010 and 2016 in routine clinical practice (aged ≥18 years at initiation) following failure of first-line chemotherapy were eligible. Data were collected from hospital medical records between May 2016 and July 2016, on all episodes of confirmed or suspected NS related to docetaxel monotherapy, including patient characteristics. Episodes of confirmed NS were defined as documented absolute neutrophil count $< 1.0 \times 10^9$/L, plus temperature > 38 °C or other signs/symptoms of sepsis, otherwise episodes were classified as suspected NS.

Results: 121 patients were included (median age 65.5 years; 57.9% male; median 4.0 cycles of docetaxel; 19.8% treated with prophylactic granulocyte-colony stimulating factor). Episodes of confirmed or suspected NS were recorded in 21/121 (17.4%) patients (11 confirmed episodes in 11 [9.1%] patients and 11 suspected episodes in 10 [8.3%] patients). Resource utilisation data were available for 21/22 episodes; the mean length of stay for confirmed NS admissions (n = 11) was 9.2 (SD: 9.2) days and for suspected NS admissions (n = 10) was 4.7 (SD: 4.6) days. The most commonly prescribed treatment for NS was piperacillin/tazobactam therapy (46.5% of all documented treatments). The mean total costs of managing patients with confirmed NS (n = 11) and suspected NS (n = 9) were £3163 (SD: £2921) and £1790 (SD: £1585) per patient, respectively.

Conclusion: Rates of confirmed NS in UK clinical practice were broadly similar to those reported in clinical trials; however, the burden of suspected NS, not routinely reported elsewhere, is also substantial.

1. Introduction

The recommended first-line treatment for the majority of patients with advanced non-small cell lung cancer (NSCLC) is a platinum-based chemotherapy regimen. Docetaxel monotherapy was the accepted standard of care for more than a decade for second-line therapy in

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; GAfREC, Governance Arrangements for Research Ethics Committees; G-CSF, granulocyte colony stimulating factor; IQR, interquartile range; LOS, length of stay; NICE, National Institute for Health and Care Excellence; NS, neutropenic sepsis; NSCLC, non-small cell lung cancer; SD, standard deviation

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unselected patients with NSCLC relapsing after first-line therapy [1,2]. However, docetaxel is associated with numerous haematological and non-haematological adverse events, including diarrhoea, nausea, vomiting, anaemia, neutropenia and neutropenic sepsis (NS; also known as febrile neutropenia) [3]. Although docetaxel monotherapy remains the benchmark by which other second-line treatments are evaluated, a number of newer therapies for NSCLC have demonstrated benefit in terms of endpoints such as progression-free survival, overall survival and toxicity when used either alone or in combination [2,4,5].

NS is a serious and life-threatening complication of chemotherapy requiring urgent intervention. Therefore all patients presenting with confirmed or suspected NS are treated as a medical emergency with empiric broad-spectrum antibiotic therapy; ongoing treatment is dependent upon the assessment of risk for developing septic complications [6–8]. A meta-analysis of randomised controlled trial data reported the incidence of confirmed NS in patients with NSCLC treated with docetaxel monotherapy as 5.95% (95% CI: 4.22–8.31) [9]. However, there are limited data on the incidence of confirmed and suspected episodes of NS in patients with NSCLC treated with docetaxel monotherapy in the real world clinical setting [10]. It remains unclear what the true burden of confirmed and suspected episodes of NS following docetaxel monotherapy is in patients with NSCLC and what associated healthcare resources are required for their management.

The primary objective of this study was to describe the rate of NS in patients with NSCLC treated with docetaxel monotherapy following relapse after first-line therapy in a 'real world' UK clinical practice setting. Other study objectives were to describe the rate of suspected NS, and the NHS resource utilisation and healthcare system cost burden associated with management of patients with NSCLC presenting with confirmed or suspected NS.

2. Materials and methods

2.1. Study design and setting

This study was a multi-centre, retrospective, observational research study of patients with NSCLC treated with docetaxel monotherapy following failure of first-line therapy. It was conducted in seven secondary or tertiary care centres in England and Wales (ClinialTrials.gov reference NCT02658747). Centres routinely treating NSCLC patients with docetaxel monotherapy following relapse after first-line chemotherapy, and where patients were likely to present to the same Trust for management of docetaxel-related toxicities were selected. Data were collected between May 2016 and July 2016. This study is reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) statement [11].

2.2. Patient selection

Adult patients with stage III or IV NSCLC initiated on docetaxel monotherapy (aged $\geq$18 years at initiation) after progression or intolerance to at least one line of prior chemotherapy who were initiated on docetaxel $\leq$6 years prior to data collection and who received the last dose of docetaxel $\geq$30 days prior to data collection were eligible for inclusion. Patients receiving docetaxel monotherapy as part of a clinical trial and those with no data on absolute neutrophil count (ANC) were excluded from the study. Sequential patients were identified from chemotherapy prescribing data and eligible patients selected in reverse chronological order of docetaxel monotherapy initiation until the target sample size had been reached (with a maximum of 25 patients at each centre) to minimise bias in selecting patients and ensure that data collected reflected recent clinical practice. Data were collected from patients' medical records by the clinical care team and therefore under the Governance Arrangements for Research Ethics Committees (GAfREC, 2012) research ethics committee approval and patient consent were not required [12].

2.3. Outcome measures and definitions

The primary outcome measure was the proportion of patients with a confirmed episode of NS at presentation. There are a variety of NS definitions used in guidelines and clinical protocols [6,8,13,14]. Consistent with the variability in international guidelines, a UK national audit of clinical protocols identified local variations in the definition of neutropenic sepsis; 67% of protocols used a cut-off point for ANC of $< 1.0 \times 10^9$/L, 89% of protocols specified temperature cut-off points that included either one or two temperature recordings $>$ 38.0 °C, and 71% of protocols indicated that clinical signs of sepsis should also be considered [13]. To ensure consistency between centres, episodes of NS recorded in patients' medical records for which treatment was initiated were classified as confirmed NS if the recorded ANC at presentation was $< 1.0 \times 10^9$/L, and the recorded temperature was $>$ 38 °C or other signs and symptoms consistent with clinically significant sepsis were documented. All other episodes of NS for which treatment was initiated that did not meet the criteria for confirmed NS at presentation (e.g. episodes where treatment was initiated based only upon an ANC below the cut-off point, or where treatment was initiated based upon temperature above the cut-point and/or clinical suspicion of sepsis with no ANC below the cut-off point) were classified as clinically suspected NS.

Secondary outcome measures included: the distribution of all haematological toxicities (NS, anaemia, thrombocytopenia, neutropenia, pancytopenia); the proportion of patients with an episode of NS when defined as an absolute neutrophil count of $< 0.5 \times 10^9$/L and either a temperature $>$ 38 °C or other signs/symptoms consistent with clinically significant sepsis; the proportion of patients experiencing one or more episodes of confirmed or clinically suspected NS; and hospital resource use associated with management of confirmed or clinically suspected NS (including hospital attendances and admissions, investigations and treatment).

2.4. Data collection

Data were collected on patient demographic and clinical characteristics at docetaxel initiation (including age, sex, disease history, docetaxel dosing, prophylactic granulocyte colony stimulating factor [G-CSF] treatment) and details of all episodes of confirmed or suspected NS (including details of ANC, temperature and documentation of clinical signs and symptoms of NS at the time of presentation; NS-related attendances/admissions and length of stay [LOS]; NS-related treatment and investigations). Data on episodes of confirmed or suspected NS were collected from the date of initiation of docetaxel monotherapy until 30 days after the end of docetaxel treatment unless patients were hospitalised for docetaxel-related toxicity for longer than 30 days after docetaxel discontinuation in which case data were collected until the date of discharge or death (whichever was sooner).

2.5. Cost analysis

A monetary value (UK GBP) was assigned to the following resources: hospital attendances/admissions, antibiotic and G-CSF prescribing. The costs of prescribed medicines were calculated using unit costs published in the British National Formulary volume 71 [15]. Costs for hospital admissions/attendances were calculated based on the ward description for the admission or type of attendance using unit costs published in the NHS National Tariff Payment System [16] and NHS Reference Costs [17]. Mean costs of managing NS were compared with previously reported studies after adjusting for currency and inflation using the Campbell and Cochrane Economics Methods Group and Evidence for Policy and Practice Information and Co-ordination Centre Cost Converter [18].