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Original Article

Evaluation of a 'Watch and Wait' Approach for Chemotherapy in Patients with Newly Diagnosed Advanced Non-small Cell Lung Cancer from a Diverse Community Population

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Abstract

Aims: Systemic therapy in advanced non-small cell lung cancer (NSCLC) is the standard of care. The time of treatment administration has not been examined in the metastatic setting. A 'watch and wait' approach for the initiation of chemotherapy is sometimes used in clinical practice, either because of patient preference, presumed indolent disease behaviour, upfront radiotherapy or other interventions. We propose to evaluate the effect of a watch and wait approach on systemic treatment deliverability and patients' outcomes in a population-based study.

Materials and methods: A retrospective analysis of stage IIIB/IV NSCLC patients referred to medical oncology at the British Columbia Cancer Agency in 2009 was conducted. We defined the following: immediate chemotherapy (ICT) – chemotherapy ≤8 weeks from medical oncology consult; watch and wait chemotherapy (WWC) – initial observation with chemotherapy > 8 weeks from medical oncology consultation; watch and wait missed (WWM) – watch and wait patients who did not receive chemotherapy; best supportive care (BSC) – patients deemed chemotherapy ineligible. Statistical methods included Kaplan–Meier analysis, Log-rank tests and Cox proportional hazards modelling.

Results: In total, 744 patients were seen by medical oncology; 355 (48%) received ICT, 173 (23%) watch and wait and 216 (29%) BSC. Of the 173 patients on a watch and wait approach, 42% missed an opportunity for chemotherapy due to poor performance status (50%), death (49%) and comorbidity (1%). The median overall survival was as follows: watch and wait 11.5 months, ICT 12.8 months and BSC 4.3 months ($P < 0.0001$). Controlling for confounding factors (age, gender, performance status), overall survival was longer in WWC (hazard ratio 0.73, confidence interval 0.81–1.07, $P = 0.023$) and lower in WWM (hazard ratio 1.68, 95% confidence interval 1.27–2.22, $P < 0.0001$), compared with ICT.

Conclusions: A significant proportion of watch and wait patients never receive systemic therapy, predominantly due to a decline in performance status. Patients in the ICT group were younger, had a better performance status and had non-squamous histology compared with the watch and wait group. The overall survival was longer in the patients who received ICT versus watch and wait. The watch and wait strategy is associated with a high risk of missing the opportunity for any chemotherapy and should be judiciously implemented only in carefully selected patients.

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Key words: Advanced non-small cell lung cancer; chemotherapy; surveillance; watch and wait

Introduction

Lung cancer is the most common cause of cancer deaths in both men and women, with an estimated 224 000 new cases and 159 000 deaths in the USA in 2014 [1]. Eighty-five per cent of lung cancer cases are non-small cell lung cancer (NSCLC) and of these 75% are diagnosed as advanced NSCLC [2–4].

The treatment of advanced NSCLC involves palliative systemic therapy and radiotherapy [5–9]. Targeted therapy is recommended in tumours harbouring epidermal growth factor receptor (*EGFR*) mutations or an anaplastic lymphoma cell kinase (*ALK*) fusion oncogene, whereas a platinum-doublet is first-line therapy in *EGFR*- and *ALK*-negative patients [10]. For most patients, immediate commencement of systemic therapy is recommended to avoid performance status decline and a missed opportunity for chemotherapy.

In clinical practice, physicians may consider a 'watch and wait' strategy in selected patients with a low-burden of

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disease, who are asymptomatic, demonstrate indolent biology or whose disease was effectively palliated with radiotherapy. One of the main concerns of a watch and wait approach is that patients may miss out on a window of opportunity to receive treatment. In the first-line setting, a missed opportunity for chemotherapy results in an inability to receive any subsequent lines of active chemotherapy, thereby significantly compromising survival. With best supportive care (BSC), the median overall survival is only 4.5 months, which highlights how quickly patients may decline in the absence of active treatment and therefore the risk inherent with a watch and wait approach [11–13].

There have been no clinical trials designed to specifically evaluate the timing of first-line systemic therapy administration. Some insights may be gained from the Fidias *et al.* trial [14], which evaluated immediate versus delayed docetaxel, after partial response or stable disease with first-line cisplatin and gemcitabine. In the intention to treat analysis there was a trend towards detriment in the delayed arm, with an overall survival of 9.7 months versus 12.3 months in the immediate docetaxel arm. However, if the patients actually received delayed docetaxel the overall survival was 12.5 months. This suggests that regardless of timing, if therapy is delivered there is a similar survival benefit. Notably many of the delayed arm patients had deterioration and were unable to receive docetaxel at the time of progressive disease.

We sought to evaluate the effect of a watch and wait approach in clinical practice on systemic treatment deliverability and patients' outcomes in a retrospective review of our advanced NSCLC population. Our objectives were to characterise patients managed with a watch and wait strategy; to determine the proportion of patients who subsequently receive chemotherapy; and to assess the effect on survival of the watch and wait strategy.

Patients and Methods

A retrospective review was conducted of all patients referred to the British Columbia Cancer Agency with stage IIIB/IV NSCLC from 1 January 2009 to 31 December 2009 who were evaluated by a medical oncologist. Patient demographics, tumour characteristics, treatment recommendations and outcomes were extracted from patients' electronic records and the Outcomes and Surveillance Integrated System (OaSIS). Performance status was recorded at the time of initial medical oncology consultation. Ethical approval for the study was obtained from the governing research ethics board.

Medical oncology consultation notes were reviewed and treatment intent was extracted. The BSC group was defined as those patients in whom chemotherapy was unsuitable due to a poor performance status or comorbidities per the clinician. A watch and wait strategy was defined as a decision not to initiate immediate palliative chemotherapy. Immediate chemotherapy (ICT) was defined as chemotherapy less than or equal to 8 weeks from the medical oncology consultation. Watch and wait chemotherapy (WWC) was defined by an initial period of observation with chemotherapy initiation occurring greater than 8 weeks from the medical oncology consultation. Watch and wait missed (WWM) was defined as patients who were on a watch and wait strategy who missed an opportunity to receive chemotherapy before death. Patients in the watch and wait group who remained on surveillance at the time of analysis were classified as watch and wait surveillance (WWS). Watch and wait lost to follow-up (WWL) included patients for whom no follow-up data were available.

Patients in the ICT group were seen by a medical oncologist every 3 weeks, with radiological investigations per the practice of the treating physician. Patients in the watch and wait group were seen in follow-up at intervals determined at the discretion of the treating physician and varied depending on patterns of practice.

Chi-squared and Wilcoxon tests were used to compare characteristics between groups. *P*-values were two-sided, with a significance level of 0.05. Overall survival was defined as the time from stage IIIB/IV NSCLC diagnosis to death from any cause and was estimated using the method of Kaplan–Meier. The Log-rank test was used to compare overall survival between groups. Cox proportional hazards regression analysis was used to compare the ICT, WWC + WWS and WWM + WWL groups while adjusting for demographic and prognostic covariates. Factors associated with WWM were evaluated by logistic regression. The cut-off date for the final analysis was 31 March 2014. All analyses were carried out with SPSS version 14.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Evaluation of the Whole Study Cohort

We identified 744 patients with stage IIIB/IV NSCLC from the British Columbia Cancer Agency database for this 1 year period. Because *EGFR* mutation analysis was implemented in British Columbia in 2010 and *ALK* testing started in 2013, molecular status was not available for these patients and first-line targeted therapy for these driver mutations was not yet the standard of care. The patient electronic record was reviewed to assess the management strategy used by the medical oncologist (Figure 1). Of these patients, 355 (48%) received ICT, 216 (29%) were unsuitable for chemotherapy and received BSC and 173 (23%) were managed with an initial watch and wait strategy. The reasons for a watch and wait strategy included: immediate radiotherapy ($n = 110$, 64%), asymptomatic status ($n = 33$, 19%), asymptomatic multifocal lung disease ($n = 12$, 7%), patient choice ($n = 10$, 6%), pleural effusion management ($n = 6$, 4%), unknown ($n = 2$, 1%) (Figure 1).

Of the 173 patients in the watch and wait group, 57 (33%) received subsequent chemotherapy (WWC), 36 (21%)

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