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Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052) ☆

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Abstract ***Background:*** This was a prospective phase II study of cisplatin and bortezomib (CB) in the first line treatment of malignant pleural mesothelioma (MPM) with validation of progression free survival rate at 18 weeks (PFSR-18)[1] as primary end-point.
Methods: Chemotherapy-naïve patients with histologically proven MPM and performance status (PS) 0/1, were treated with cisplatin 75 mg/m^2 on day 1 and bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 every 3 weeks. The primary end-point validation utilised the landmark method.
Results: Between 2007 and 2010 82 patients were entered. PFSR-18 was 53% (80% confidence intervals, CIs, 42–64%). The overall survival (OS) was 13.5 months (95% CI 10.5–15) with 56%

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(95% CI 44–66%) alive at 1 year. The median PFS was 5.1 months (95% CI 3.3–6.5) and the response rate was 28.4% (95% CI 18.9–39.5%).
The most frequent grade 3–4 toxicities were hyponatremia (46%), hypokalaemia (17%), fatigue (12.2%), thrombocytopenia (11%), neutropenia (9.7%) and neurotoxicity (motor, sensory, other: 1.2%, 8.5%, 2.4%). There were two toxic deaths (32 and 74 days) due to acute pneumonitis and cardiac arrest.
End-point validation showed that patients with no progression/progression at 18 weeks had median OS of 16.9/11.9 months, respectively. Hazard ratio was 0.46 (CI 0.32–0.67), logrank test and C-index were 0.007 and 0.60.
Conclusion: The 50% PFSR-18 for CB was contained within the 80% CI for (42–64%). Therefore the null hypothesis could not be rejected. Accordingly this combination does not warrant further investigation. PFSR-18 was confirmed as a strong predictor of survival.

1. Introduction

There is a need for new therapeutic approaches to the treatment of malignant pleural mesothelioma (MPM) due to its increasing incidence and limited treatment options. Few patients are suitable for radical surgery.[2] Palliative surgery may be of some value but its true role needs to be defined in controlled trials.[3] Radiotherapy can control some symptoms but has a limited role.[4,5] Chemotherapy is an effective palliative treatment for patients with MPM. A cisplatin combination is superior to cisplatin alone,[6,7] with response rate (RR) of 10–20% and 20–40% for single agent and combinations, respectively. The anti-folate pemetrexed was the first licensed drug in combination with cisplatin for MPM and this regimen is now considered the standard of care for this disease in patients with performance status 0 or 1. Unfortunately, less than a half of patients respond to this regimen and the median progression free survival is only 5.7 months.

The biological mechanisms of carcinogenesis of MPM remain unknown. Several mechanisms have been suggested including activation of the nuclear factor-kappaB (NF-κB) pathway via phosphoinositide 3-kinase (PI3K), and mutational loss of NF2. NF-κB is thought to be activated in mesothelioma by chronic inflammation and real or functional loss of the NF2 gene. Bortezomib is a small molecule proteasome 20S inhibitor developed as a novel agent to treat human malignancies.[8] By inhibiting the single proteasome molecular target, bortezomib affects multiple signalling pathways. The antineoplastic effect includes inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Bortezomib also induces mitochondrial apoptosis in cells by a mechanism involving the B cell lymphoma 2 (BCL-2) family.[9]

In mesothelioma cell line treatment with bortezomib induced cell arrest in G2M phase, while it increased expression of cyclin-dependent kinase inhibitor p21 and the pro-apoptotic protein Bax.[10] Pre-treatment of mesothelioma cells with bortezomib showed synergistic effect in combination with cisplatin.[10] Bortezomib also decreases the activity of NF-κB and has demonstrated both *in vitro* and *in vivo* antitumour activity in mesothelioma cell lines.[11] Bortezomib, however, exhibited limited activity as a single agent in the second line treatment of patients with MPM (response rate 5%).[12]

Adoption of uni-dimensional measurement standards as outlined by the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines should make tumour response in MPM studies more meaningful.[13] Byrne et al. described a similar method of response evaluation using uni-dimensional measurement of the tumour at three separate levels on cross-sectional computed tomography (CT) scan.[14]

Several phase II studies in MPM have been conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group. A pooled analysis of these studies[1] suggested that progression free survival rate at 18 weeks (PFSR-18) was a meaningful parameter in the monitoring of new drug activity in mesothelioma[1] and therefore was chosen as the primary end-point in this study.

The aim of the study was to establish whether cisplatin and bortezomib (CB) exhibit significant efficacy in chemo naïve patients with MPM on the basis of PFSR-18. In addition, this study was also intended to validate PFSR-18 as an end-point for phase II studies in MPM.

2. Materials and methods

This was a single arm phase II study in patients with histologically proven MPM (including mixed and sarcomatoid subtypes), recurrent/not suitable for radical surgery. Patients were: age $\geqslant$18 years, World Health Organisation (WHO) performance status (PS) 0–1, life expectancy >12 weeks and appropriate cardiac function. Measurable or evaluable disease according to modified RECIST was required and patients had, adequate haematological (absolute neutrophil count (ANC) count $>1.5 \times 109$/L, platelets $>100 \times 109$/L), renal (creatinine clearance: >60 ml/min [Cockroft and Gault formula] or