Lung Cancer 76 (2012) 354–361

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Trabectedin in patients with advanced non-small-cell lung cancer (NSCLC) with XPG and/or ERCC1 overexpression and BRCA1 underexpression and pretreated with platinum

Bartomeu Massuti[a], Manuel Cobo[b], Carlos Camps[c], Manuel Dómine[d], Mariano Provencio[e], Vicente Alberola[f], Nuria Viñolas[g], Rafael Rosell[h], Miguel Tarón[i], Vanesa Gutiérrez-Calderón[b], Pilar Lardelli[j], Vicente Alfaro[j], Antonio Nieto[j], Dolores Isla[k,*]

[a] *Hospital General Universitario de Alicante, Alicante, Spain*
[b] *Hospital Regional Universitario Carlos Haya, Málaga, Spain*
[c] *Hospital General Universitario de Valencia, Valencia, Spain*
[d] *Fundación Jiménez Díaz, Madrid, Spain*
[e] *Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*
[f] *Hospital Arnau de Vilanova, Valencia, Spain*
[g] *Hospital Clínic i Provincial de Barcelona, Barcelona, Spain*
[h] *Hospital Germans Trias I Pujol, Badalona, Spain*
[i] *Pangaea Biotech S.A. USP Institut Universitari Dexeus, Barcelona, Spain*
[j] *PharmaMar, Clinical R&D, Colmenar Viejo, Madrid, Spain*
[k] *Hospital Clínico Lozano Blesa, Zaragoza, Spain*

ARTICLE INFO

Article history:
Received 29 September 2011
Received in revised form 2 December 2011
Accepted 4 December 2011

Keywords:
NSCLC
Lung
Gene signature
Chemotherapy
Response
Trabectedin

ABSTRACT

Background: Previous studies in sarcoma found that a composite gene signature, including high expression of nucleotide excision repair (NER) genes (XPG and/or ERCC1) and low expression of homologous recombination repair (HR) genes (BRCA1), identifies a highly sensitive population of patients with significantly improved outcome to trabectedin. This exploratory phase II trial evaluated a customized trabectedin treatment according to this gene signature in patients with non-small cell lung cancer (NSCLC) after the failure of standard platinum-based treatment.
Methods: Patients were selected according to their mRNA expression (elevated XPG and/or ERCC1, with low BRCA1) using the following values as cutoff: XPG = 0.99, ERCC1 = 3.47 and BRCA1 = 12.00. Trabectedin was administered as a 1.3 mg/m^2 3-hour intravenous infusion every 3 weeks (q3wk). The primary efficacy endpoint was the progression-free survival rate at 3 months. Objective response according to the Response Evaluation Criteria in Solid Tumors (RECIST) was a secondary efficacy endpoint.
Results: Two of 18 evaluable patients (11.1%; 95% CI, 1.38–34.7%) achieved progression-free survival rate at 3 months. The primary efficacy objective (at least 3 of 18 patients being progression-free at 3 months) was not met, and therefore the trial was early finalized. No objective responses per RECIST were achieved. Four patients had stable disease. Median PFS was 1.3 months, and median overall survival was 5.9 months. Trabectedin was usually well tolerated, with a safety profile similar to that described in patients with other tumor types.
Conclusions: Customized treatment with trabectedin 1.3 mg/m^2 3-h q3wk according to composite gene signature (XPG and/or ERCC1 overexpression, and BRCA1 underexpression) was well tolerated, but had modest activity in NSCLC patients pretreated with platinum. Therefore, further clinical trials with trabectedin as single agent in this indication are not warranted.

1. Introduction

Trabectedin is a marine-derived antineoplastic agent, initially isolated from the tunicate *Ecteinascidia turbinata* and currently produced synthetically, which has shown antitumor activity in different neoplastic diseases, such as advanced soft tissue sarcoma (STS) [1–3], relapsed ovarian cancer [4–8], metastatic

* Corresponding author at: Servicio de Oncología Médica, Hospital Clínico Lozano Blesa, Avda San Juan Bosco, 15, 50009 Zaragoza, Spain. Tel.: +34 97 676 5746; fax: +34 97 635 4212.
E-mail address: lola.isla@gmail.com (D. Isla).

0169-5002/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2011.12.002

hormone-refractory prostate cancer [9], and advanced breast cancer [10,11]. Trabectedin is approved in Europe for the treatment of patients with advanced STS after failure of anthracyclines or ifosfamide, or who are unsuited to receive these agents [12], and combined with pegylated liposomal doxorubicin for the treatment of patients with relapsed, platinum-sensitive ovarian cancer [7].

Several preclinical findings indicated non-small cell lung cancer (NSCLC) as an interesting target for evaluation in clinical trials. An *in vitro* evaluation against the panel of human tumor lines of the National Cancer Institute (NCI) detected activity of trabectedin at concentrations between 0.3 and 0.5 ng/ml against NSCLC [13]. Comparative analysis of trabectedin showed a COMPARE profile similar to that of other DNA-intercalating agents, such as anthracyclines and morpholine [14]. Trabectedin was found active against NSCLC specimens in studies based on tumoral colony-forming units recently obtained from human solid tumors. At 100 nM and at 1 μM, trabectedin inhibited 69% (9/13) and 85% (11/13) of NSCLC specimens, respectively [15]. Trabectedin was also found active in human NSCLC LXFL 529 xenografts implanted in mice [16]. In addition, trabectedin did not show complete cross-resistance with paclitaxel, cisplatin, or other agents routinely used in NSCLC treatment [15].

Trabectedin's mechanism of action is different from that of other available DNA-damaging agents used in cancer chemotherapy [17]. Trabectedin has a chemical structure characterized by three fused tetrahydroisoquinoline rings: two of them provide the framework for covalent interaction with the minor groove of the DNA double helix, whereas the third ring protrudes from the DNA duplex, allowing interactions with adjacent nuclear proteins. Then, trabectedin causes a helix distortion bending of the DNA molecule towards the minor groove [18], a lesion that is recognized by the nucleotide excision repair (NER) pathway. The NER endonuclease XPG covalently binds to the third subunit of trabectedin. Therefore, interaction between trabectedin and XPG seems to confer increased sensitivity to this compound [19], and crosstalk between NER and homologous recombination repair (HR) pathways deals with trabectedin-induced lesions. The antiproliferative effects of trabectedin in tumor cells are mediated by the NER pathway (XPG being the main NER protein involved) and the HR pathway would act as a survival mechanism converting the death-inducing ternary complex NER-trabectedin-DNA into double strand breaks (DSBs) that could be repaired by HR, resulting in cell survival. Cells deficient in HR are more sensitive to trabectedin because of the persistence of DNA lesions and increased formation of replication-dependent DSBs [20]. BRCA1 and ERCC1, key regulators involved in DNA end resection during HR, are part of the *in vitro* expression signature of genes associated with sensitivity to trabectedin treatment [21,22].

Efforts have been done to determine a gene signature predictive of sensitivity to trabectedin by correlating *in vitro* efficacy data with corresponding gene expression. A signature of 19 gene transcripts was identified to predict sensitivity to trabectedin, which significantly discriminated responsive tumors, including STS and ovarian cancer, but also lung cancer, pleural mesothelioma, head and neck, breast and pancreas cancer [23]. In contrast to the gene profile predicting efficacy with platinum salts and anthracyclines, increased expression of XPG protein or mRNA is correlated to a better outcome with trabectedin treatment [24]. Further studies proved that a composite gene signature (low BRCA1, and high XPG and/or ERCC1) identifies a highly sensitive population of STS patients with significantly improved outcome to trabectedin treatment [25,26].

BRCA1 and ERCC1 are widely studied genes at the level of both RNA and protein expression, which are associated with the prognosis and prediction of response to anticancer compounds [27,28]. Low BRCA1 expression has been associated to paclitaxel resistance [29], and high ERCC1 expression has been associated to a less favorable clinical response in NSCLC patients treated with gemcitabine/cisplatin [28,30]. Furthermore, the treatment of NSCLC patients with platinum-based regimens increases the expression of NER genes [31,32]. Therefore, the use of the molecular signature of low BRCA1 expression and high XPG and/or ERCC1 expression might allow the identification of NSCLC pretreated patients likely to be responders to trabectedin. Approximately one third of NSCLC patients may have the trabectedin-sensitive phenotype, *i.e.*, low BRCA1 mRNA expression and high XPG and/or ERCC1 mRNA expression. This population may also correspond to patients resistant to taxanes (due to low BRCA1 expression) and to gemcitabine/cisplatin (due to high ERCC1 or XPG expression), which are the current standard treatments in NSCLC.

The aim of this open-label, non-comparative, exploratory phase II clinical trial was to evaluate the efficacy and safety of trabectedin in patients with NSCLC, who have overexpression of NER genes (XPG and/or ERCC1), and underexpression of HR genes (BRCA1), after the failure of standard platinum-based treatment.

2. Materials and methods

Patients were recruited at 8 Spanish investigational sites. The study protocol was approved by the Independent Local Ethics Committee of each participating center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations on clinical trials. Signed informed consent was obtained from all patients prior to any study-specific procedure.

2.1. Eligibility criteria

Eligibility criteria included patients ≥18 years old with histological diagnosis of non-resectable or metastatic, locally advanced, recurrent or persistent NSCLC after a previous line of platinum-based cytotoxic chemotherapy, who had overexpression of XPG and/or ERCC1, and underexpression of BRCA1. Patients had to have at least one unidimensionally or bidimensionally lesion measurable by computed tomography, located in non-irradiated areas and measured within 4 weeks before treatment. Furthermore, patients had to have life expectancy ≥3 months; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤1, complete recovery from any toxicity due to previous therapy (except for grade 1 neuropathy and/or alopecia), and adequate hematological, hepatic and renal function.

Patients were excluded if they had received chemotherapy or therapy with biological agents within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment onset; previous treatment with more than one line of platinum-based chemotherapy for advanced disease (neoadjuvant or adjuvant therapy allowed); contraindications for the use of corticosteroids; history of prior malignancies (except for skin cancer other than melanoma or cervical carcinoma *in situ* adequately treated); cerebral and/or leptomeningeal metastases; uncontrolled pleural effusion; history of severe cardiac disease or uncontrolled arterial hypertension within one year before study entry; active infection; active liver disease, major surgery within 2 prior weeks, or any other unstable or serious medical condition. Patients were also excluded if they were pregnant or breast-feeding women, or if they were not using appropriate contraceptive measures.

2.2. Tumor samples and pathological evaluation

Formalin-fixed, paraffin-embedded tumor specimens were cut in two 4-μm sections, one of which was placed on a standard slide and the other on a penmembrane slide. The percentage of tumor