European Journal of Cancer 86 (2017) 385–393

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Phase II, multicentre, randomised trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy in patients with HER2-negative metastatic breast cancer

Yeon Hee Park [a,1], Seock-Ah Im [b,1], Sung-Bae Kim [c], Joo Hyuk Sohn [d], Keun Seok Lee [e], Yee Soo Chae [f], Ki Hyeong Lee [g], Jee Hyun Kim [h], Young-Hyuck Im [a], Ji-Yeon Kim [a], Tae-Yong Kim [b], Kyung-Hun Lee [b], Jin-Hee Ahn [c], Gun Min Kim [d], In Hae Park [e], Soo Jung Lee [f], Hye Sook Han [g], Se Hyun Kim [h], Kyung Hae Jung [c,*], Korean Cancer Study Group (KCSG)

[a] *Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, North Korea*
[b] *Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University, College of Medicine, Seoul, North Korea*
[c] *Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, North Korea*
[d] *Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, North Korea*
[e] *Center for Breast Cancer, National Cancer Center, Goyang, North Korea*
[f] *Kyungpook National University Medical Center, Daegu, North Korea*
[g] *Chungbuk National University Hospital, Cheongju, North Korea*
[h] *Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, North Korea*

Received 10 August 2017; received in revised form 13 September 2017; accepted 1 October 2017

KEYWORDS
Metastatic breast cancer;
Eribulin;

Abstract ***Background:*** Paclitaxel plus gemcitabine (PG) combination chemotherapy is a preferred chemotherapeutic regimen for patients with metastatic breast cancer (MBC). Eribulin mesylate is a halichondrin non-taxane inhibitor of microtubule dynamics. A recent pooled analysis with eribulin showed improved overall survival (OS) in various MBC patient

* *Corresponding author*: Division of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, North Korea. Fax: +82 2 3010 6961.
E-mail address: khjung@amc.seoul.kr (K.H. Jung).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejca.2017.10.002

Paclitaxel;
Gemcitabine;
Chemotherapy

subgroups pretreated with anthracycline and taxane. Furthermore, eribulin may have less neurotoxicity than paclitaxel.

Patients and methods: This study was a prospective randomised phase II, open-label, two-arm, multicentre study comparing eribulin plus gemcitabine (EG) with PG chemotherapy as a first-line treatment for patients with human epidermal growth factor receptor 2-negative MBC. We hypothesised that EG chemotherapy would not be inferior to PG chemotherapy. The primary end-point was progression-free survival (PFS), which was estimated to be 70% at 6 months for each arm. The secondary end-points were as follows: OS, neuropathic scale, toxicity and clinical benefit rate.

Results: A total of 118 patients (median age: 50, 24–66) were enrolled between March 2015 and March 2016 and were randomly assigned to PG ($n = 59$) or EG ($n = 59$) chemotherapy. The mean number of metastatic sites was 3 (range 1–8). The 6-month PFS rates for both arms were 72% for EG and 73% for PG ($P = 0.457$). There was no significant difference in OS between the two groups (not reached versus 21.2 months, $P = 0.2234$). The median number of chemotherapy cycles for both groups was 10 for EG and 8 for PG (range 2–32). Clinical benefit rates were 44% for EG and 49% for PG. Major toxicities were neutropenia and neurotoxicity. Grade II or above neurotoxicity was more common with PG than with EG (13.6% for EG versus 45.8% for PG, $P < 0.0001$).

Conclusion: EG chemotherapy had similar clinical benefits to PG chemotherapy in terms of PFS but less neurotoxicity.

Trial registration: KCSG BR13-11; ClinicalTrials.gov, NCT02263495.

1. Introduction

Breast cancer (BC), the most frequent malignancy in women, is a global problem and a leading cause of cancer mortality worldwide including Korea [1,2]. Metastatic BC (MBC) continues to be an incurable disease with a poor prognosis and a median 5-year survival of only 23–26% [1,3]. Effective long-term management of MBC poses significant clinical challenges. Taxanes, such as paclitaxel and docetaxel, are a cornerstone treatment across multiple lines of therapy to improve survival duration and palliate symptoms while minimising toxicity and maintaining quality of life (QoL) for patients with MBC.

Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics and is in the halichondrin class of antineoplastic drugs. Eribulin has a novel mode of action that is distinct from those of other tubulin-targeting agents, inhibiting the microtubule growth phase without affecting the shortening phase and causing tubulin to be sequestered into non-productive aggregates [4–6]. A recent pooled analysis showed an improvement in survival when eribulin was used with anthracycline in various subgroups of MBC patients pretreated with taxane [7]. Preclinical studies have found that eribulin combines synergistically with gemcitabine to induce tumour regression in non-small cell lung cancer xenografts [8,9]. Eribulin plus gemcitabine (EG) combination may be a potentially new regimen for early-line therapy in patients with MBC.

The phase III trial of paclitaxel and gemcitabine (PG) combination versus paclitaxel alone proved that gemcitabine added to paclitaxel is an effective therapy for women with BC who have previously received anthracyclines [10]. PG combination chemotherapy is one of the preferred chemotherapeutic regimens for patients with MBC and was found to be an appropriate maintenance chemotherapy regimen with survival benefits and a feasible toxicity profile in a large phase III Korean Cancer Study Group (KCSG) study [11].

Although there is no direct evidence that eribulin has a better neurotoxic profile than taxane, eribulin tended to show less neurotoxicity compared with ixabepilone in a phase II trial [12].

Chemotherapy-induced neurotoxicity is a significant problem in patients treated with taxane. Although there is no direct evidence that eribulin has a better neurotoxicity profile than taxane, there is some indirect evidence. Wozniak *et al.* conducted a mouse study to compare the neuropathy-inducing propensity of three drugs: paclitaxel, ixabepilone and eribulin mesylate [12]. Paclitaxel and ixabepilone, at their respective maximal tolerable doses, produced significant deficits in caudal nerve conduction velocity, caudal amplitude and digital nerve amplitudes as well as moderate to severe degenerative pathologic changes in dorsal root ganglia and the sciatic nerve. In contrast, eribulin mesylate produced no significant deleterious effects on any nerve conduction parameter measured and caused milder, less frequent effects on morphology. The toxicity of eribulin is no