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Original Research

Development of peripheral neuropathy and its association with survival during treatment with *nab*-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: A subset analysis from a randomised phase III trial (MPACT)

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Abstract ***Background:*** In a phase III trial in patients with metastatic pancreatic cancer (MPC), *nab*-paclitaxel plus gemcitabine (*nab*-P/Gem) demonstrated greater efficacy but higher rates of peripheral neuropathy (PN) versus Gem. This exploratory analysis aimed to characterise the frequency, duration, and severity of PN with *nab*-P/Gem in the MPACT study.
Patients and methods: Patients with previously untreated MPC received *nab*-P/Gem or Gem. PN was evaluated using a broad-spectrum group of Standardised Medical Dictionary for

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Regulatory Activities Queries (SMQ) and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. A case report form was completed by physicians on day 1 of each cycle (also graded by NCI CTCAE version 3.0).
Results: In the *nab*-P/Gem arm, 227/421 patients (54%) experienced any-grade PN and 70 (17%) experienced grade III PN. No grade IV PN was reported. Most early-onset PN events were grade I, and treatment-related grade III PN occurred in 7% of patients who received up to three cycles of *nab*-P. Of those who developed grade III PN with *nab*-P/Gem treatment, 30 (43%) improved to grade ≤I (median time to improvement = 29 days) and 31 (44%) resumed therapy. Development of PN was associated with efficacy; median overall survival in patients with grade III versus 0 PN was 14.9 versus 5.9 months (hazard ratio, 0.33; $P < .0001$).
Conclusions: *nab*-P/Gem was associated with grade III PN in a small percentage of patients. PN development was associated with longer treatment duration and improved survival. Grade III PN was reversible to grade ≤I in many patients (median ≈ 1 month) NCT00844649.

1. Introduction

Advanced pancreatic cancer (PC) is associated with poor survival, with a 5-year survival rate of ≈2% in the United States [1]. Until recently, patients with advanced PC had limited treatment options. *nab*-Paclitaxel plus gemcitabine (*nab*-P/Gem) is a new treatment option that was approved based on the results of the phase III MPACT trial, in which *nab*-P/Gem demonstrated superiority over Gem [2]. The median overall survival (OS) for *nab*-P/Gem versus Gem was 8.5 versus 6.7 months (hazard ratio [HR], 0.72; $P < .001$), the median progression-free survival (PFS) was 5.5 versus 3.7 months (HR, 0.69; $P < .001$), and the overall response rate (ORR) by independent review was 23% versus 7% ($P < .001$). In an updated report, the final OS for *nab*-P/Gem versus Gem was 8.7 versus 6.6 months (HR, 0.72; $P < .001$) [3].

Peripheral neuropathy (PN) can be dose limiting and can persist indefinitely in some cases [4–6]. However, proper management of PN can potentially extend treatment. *nab*-P was developed to overcome the formulation limitations attributed to the solvent Kolliphor EL (formerly called Cremophor EL) and improve the safety profile and therapeutic index of solvent-based paclitaxel (sb-P) [7]. In phase II/III trials of various tumour types, *nab*-P regimens demonstrated improved efficacy and tolerability compared with solvent-based taxanes [8–10]. Compared with sb-P/carboplatin (C), *nab*-P/C was associated with significantly lower rates of grade ≥III PN in a phase III trial of patients with advanced non-small cell lung cancer (NSCLC) [10].

MPACT was the largest trial to date to evaluate a taxane combination in a large population of patients with advanced PC [2]. As expected, the combination arm was associated with a higher incidence of grade III/IV adverse events (AEs), including PN. Understanding and managing PN is an integral part of providing optimal therapy for patients with cancer; thus, the frequency, duration, and severity of PN associated with *nab*-P/Gem therapy were investigated in this exploratory analysis of the MPACT trial.

2. Patients and methods

This subgroup analysis of the phase III MPACT trial was not pre-specified in the study protocol. The study design and patient characteristics have been described previously [2]; key parameters are described below. The independent ethics committee at each participating institution approved the study. All patients provided written informed consent before the initiation of the study.

2.1. Patients

This study enrolled adult patients with a Karnofsky performance status (KPS) ≥70 and histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients were required to have adequate hepatic, haematologic, and renal function (including bilirubin level ≤ the upper limit of normal, absolute neutrophil count ≥1.5×10^9/L, and haemoglobin level ≥9 g/dl) and baseline PN grade ≤I.

2.2. Study design and treatment

Patients were randomised (1:1) to receive a 30–40-minute intravenous infusion of *nab*-P 125 mg/m^2, followed by Gem 1000 mg/m^2 on days 1, 8, 15, 29, 36, and 43, or Gem alone 1000 mg/m^2 weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, patients received treatment on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity.

2.3. Safety assessments

Investigators monitored treatment-related AEs and serious AEs; weekly central laboratory data; and rates