European Journal of Cancer 56 (2016) 162–171

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Is there a role of nab-paclitaxel in the treatment of advanced non-small cell lung cancer? The data suggest yes

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Received 16 October 2015; received in revised form 8 December 2015; accepted 21 December 2015
Available online xxx

KEYWORDS
Nab-paclitaxel;
Non-small cell lung cancer (NSCLC);
Carboplatin;
Neuropathy;
Squamous cell histology;
Elderly

Abstract Nab-paclitaxel is a novel therapeutic agent, which was approved in combination with carboplatin in the first-line treatment of advanced non-small cell lung cancer (NSCLC) regardless of histologic subtype in the United States of America by the Food and Drug Administration in 2012 and by the European Commission in 2015. This approval was based on the results of a phase III clinical trial showing superior response rates compared with solvent-based paclitaxel in combination with carboplatin. This review will focus on the early development and clinical data to date supporting the use of nab-paclitaxel in advanced NSCLC. The clinical question central to this review is whether nab-paclitaxel has a place in the current therapeutic landscape of advanced NSCLC.

Lung cancer is the leading cause of cancer mortality in the United States of America and worldwide [1]. An estimated 221,200 new lung cancer cases will be diagnosed in 2015 in the United States of America alone, and 158,040 lung cancer deaths are estimated to occur [1]. Historically, palliative chemotherapy in the metastatic non-small cell lung cancer (NSCLC) setting resulted in modest survival prolongation and preservation of quality of life (QoL) [2]. Currently, platinum agents combined most commonly with taxanes, gemcitabine, vinorelbine, or pemetrexed are the standard of care in advanced NSCLC [3]. In a large randomized clinical trial comparing four platinum-based regimens, all were associated with a similar efficacy, with overall response rates (ORRs) of about 19% and a median overall survival (OS) of 7.9 months [4]. In patients with newly diagnosed advanced NSCLC, cisplatin/pemetrexed and cisplatin/gemcitabine were associated with similar efficacy, though a histology specific survival benefit was noted in patients with non-

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http://dx.doi.org/10.1016/j.ejca.2015.12.022
0959-8049/

squamous histology with pemetrexed-based therapy, while a survival detriment was noted in patients with squamous histology [5]. In general, solvent-based paclitaxel plus carboplatin (sb-PC) is the most commonly used taxane–platinum combination in the United States of America and is associated with a 15–32% ORR and a median OS of 7.9 to 10.06 months [4,6–9].

In a recent prospective observational study that captured real-world data on patients with advanced NSCLC receiving first-line platinum-based therapies across Europe, the median OS was 10.3 months in all patients. Patients in Europe were most commonly treated with platinum/pemetrexed (37.3%), followed by platinum/gemcitabine (23.6%), platinum/vinorelbine (19.7%), and platinum/taxane (19.4%); only 7% of patients received concomitant bevacizumab [10]. While the addition of bevacizumab to sb-PC for patients with non-squamous NSCLC is associated with improved efficacy, the incorporation of bevacizumab into first-line therapy in Europe has been limited [11]. In addition, the use of bevacizumab in patients with squamous NSCLC has been associated with excess toxicity in the form of pulmonary hemorrhage [7,12] and is not routinely used in the squamous subset.

The 130-nm albumin-bound nanoparticle formulation of paclitaxel (nab-paclitaxel [Abraxane]; Celgene, Summit, NJ) is a novel therapeutic agent, which was approved in the United States of America by the Food and Drug Administration (FDA) in 2012 in combination with carboplatin in the first-line treatment of advanced NSCLC regardless of histologic subtype. This approval was based on the results of a phase III trial showing superior response rates compared with sb-PC [13]. Recently, this regimen was also approved by the European Commission in 2015. This review will focus on the early development and clinical data to date supporting the use of nab-paclitaxel in advanced NSCLC.

1. Early development

Paclitaxel, a naturally occurring complex diterpenoid extracted from the bark of the western yew, *Taxus brevifolia*, stabilizes tubulin polymer and promotes microtubule assembly effectively inhibiting mitoses, motility, and intracellular transport [14–16]. Due to limited aqueous solubility, cremophor-based paclitaxel (solvent-based paclitaxel) is formulated with a cremophor EL/ethanol vehicle [17]. Solvent-based paclitaxel is associated with severe allergic, hypersensitivity, and anaphylactic reactions in humans and animals, and premedication with steroids and H1 and H2 receptor blockers are necessary to reduce the severity of these reactions [16,18–24]. The cumulative side-effects of steroids used as a premedication may contribute to treatment-related morbidity, while the cremophor EL solvent may contribute to chronic paclitaxel-induced peripheral neuropathy [25]. Cremophor and ethanol solvent leaches plasticizers from polyvinyl chloride (PVC) bags and infusion sets in routine clinical use, and solvent-based paclitaxel must be prepared and administered in either glass bottles or non-PVC infusion systems with in-line filtration [26]. In order to deliver paclitaxel in a more safe and convenient manner, the development of taxanes with improved solubility in aqueous solutions has been of great interest [27].

The lyophilized formulation of nab-paclitaxel is comprised of albumin and paclitaxel reconstituted in 0.9% NaCl. It is devoid of any solvents or ethanol with an average particle size of 130 nm allowing for intravenous administration without risk of capillary blockage [28]. Nab-paclitaxel caused tumour regression and was associated with prolonged survival in nude mice bearing human tumour xenografts with the highest level of sensitivity in lung xenografts, followed by breast, ovarian, prostate and colon models [17]. In this preclinical model, nab-paclitaxel was significantly less toxic than solvent-based paclitaxel; the LD50 and maximum tolerated dose (MTD) for nab-paclitaxel and solvent-based paclitaxel were 47 and 30 mg/kg/d and 30 and 13.4 mg/kg/d, respectively [17]. At equitoxic doses, nab-paclitaxel was associated with more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival compared with solvent-based paclitaxel [17]. Nab-paclitaxel was also associated with higher exposure of the tumour to paclitaxel; at equal doses, tumour paclitaxel area under the curve (AUC) was 33% higher for nab-paclitaxel compared with solvent-based paclitaxel [17].

Nab-paclitaxel is comprised of a colloidal suspension of albumin and paclitaxel which likely enhances drug delivery of the cytotoxic agent to the cancer cells via a receptor-mediated transport mechanism. Transendothelial cell transport of albumin is mediated by binding of albumin to the gp60 receptor, which activates caveolin-1, resulting in formation of caveoli, which transport albumin and other plasma constituents across the endothelial cell to the interstitial space [29,30]. In support of this, the endothelial binding and transcytosis of paclitaxel are markedly higher for nab-paclitaxel compared with solvent-based paclitaxel and are abrogated by a known inhibitor of endothelial gp60 receptor/caveolar transport [17]. In addition, cremophor has been found to inhibit binding of paclitaxel to endothelial cells and albumin [17]. Therefore, the enhanced efficacy and intratumour delivery of nab-paclitaxel compared with solvent-based paclitaxel are likely from enhanced endothelial cell binding and transcytosis and inhibition of binding of paclitaxel to endothelial cells and albumin by cremophor. Another possible mechanism may be mediated by osteonectin (also known as secreted protein