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Tailoring the dosing schedule of *nab*-paclitaxel in metastatic breast cancer according to patient and disease characteristics: Recommendations from a panel of experts

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ABSTRACT

The choice of chemotherapy for patients with metastatic breast cancer (MBC) depends on disease- and patient-related factors, but there is little guidance on dosing modifications for patients unable to receive the licensed dose. *Nab*-paclitaxel is a solvent-free form of paclitaxel that uses albumin as a drug carrier and exploits endogenous albumin transport pathways to achieve enhanced drug targeting and tumour penetration with reduced toxicity. It is approved for use at a dose of 260 mg/m^2 every three weeks in adults who have failed first-line treatment for MBC and for whom standard anthracycline-based therapy is not indicated. Emerging data suggest that weekly dosing schedules of *nab*-paclitaxel may provide clinical benefit in some patients, but the utility of these alternative dosing schedules remains unclear. A panel of breast cancer experts convened to review available literature for *nab*-paclitaxel in MBC and, taking into account their clinical experience, recommended that alternative dosing schedules may be considered according to the aggressiveness of disease and patient condition as follows: 125 mg/m^2 QW 3/4 (aggressive disease and fit), 100 mg/m^2 QW 3/4 (aggressive or indolent disease and unfit). All dosing schedules were considered acceptable for fit patients with indolent disease. These recommendations are based on current evidence, and emerging data from ongoing trials may reinforce or modify the recommendations provided.

1. Introduction

Metastatic breast cancer (MBC) is prevalently metachronous and develops either as visceral disease, with or without associated bone metastases, or as bone-only disease. The choice of treatment should be individualized and is usually decided based on multiple factors, including aggressiveness of disease, previous therapies and response to them, site and extent of metastases, tumour biology and patient-related factors, such as age, comorbidities and performance status (Cardoso et al., 2012a,b). Chemotherapy represents the cornerstone of treatment for the majority of patients with MBC at some time in the course of the disease (Cardoso et al., 2012b), and although clinical practice guidelines aimed at facilitating the optimum management of MBC are available (Cardoso et al., 2012a,b), there are no definitive treatment algorithms. Furthermore, there is a lack of guidance regarding the definition of different dosing schedules of available agents in order to balance activity and safety, and to tailor treatment for each individual patient to maximise outcome.

Taxane-containing chemotherapy is a treatment of choice for many patients with MBC, and is the only standard of care first-line treatment for patients progressing after adjuvant anthracycline-based non-taxane-containing chemotherapy (Cardoso et al., 2012b). Findings from phase III trials have shown that conventional paclitaxel 175 mg/m^2 Q3W results in objective response rates (ORRs) of 25–29% (Nabholtz et al., 1996; Jones et al., 2005), whereas slightly higher ORRs are seen with docetaxel 75–100 mg/m^2 Q3W (30–48%) (Jones et al., 2005; Aapro, 1998; Nabholtz et al., 1999; Sjostrom et al., 1999). Subsequent phase III trials showed that a QW regimen of conventional paclitaxel (80–90 mg/m^2) improved ORR (Verrill et al., 2007; Seidman et al., 2008), time to progression (TTP) (Verrill et al., 2007; Seidman et al., 2008) and overall survival (OS) (Seidman et al., 2008) compared with the standard Q3W dose, whereas similar improvements were not seen with a QW regimen of docetaxel (35 mg/m^2 QW for three weeks out of every four [3/4]) (Rivera et al., 2008). As such, QW dosing of conventional paclitaxel and Q3W dosing of docetaxel are the most frequently used in routine clinical practice for the treatment of patients with MBC.

Despite the established efficacy of traditional taxanes, the poor solubility of these agents means that they are formulated using solvents, which contribute to their toxicity profile. As a result, prophylactic premedications, including antihistamines, corticosteroids and granulocyte colony-stimulating factor (G-CSF), are required to mitigate the risk of toxicity (EMA, 2011; FDA, 2005).

Nab-paclitaxel (Abraxane®) was designed to enhance the therapeutic index of conventional taxanes and represents a significant advance in taxane therapy (Desai, 2008; von Minckwitz et al., 2013). This solvent-free formulation comprises albumin-bound particles of paclitaxel, and unlike conventional paclitaxel, is thought to utilize the natural albumin binding and transport pathways, specifically gp60 and caveolin-mediated transcytosis, to achieve enhanced drug delivery to the tumour (Desai et al., 2006; Kratz, 2008) and reduced drug exposure to healthy tissue (Hawkins et al., 2003). Furthermore, as no solvent is included in its formulation, it avoids some of the acute toxicity associated with conventional paclitaxel whilst avoiding the need for corticosteroid co-administration.

In a randomized phase III trial, *nab*-paclitaxel 260 mg/m^2 Q3W significantly improved outcomes (ORR, TTP and progression-free survival [PFS]) compared with conventional paclitaxel 175 mg/m^2 Q3W in patients with MBC, with a significant improvement in OS seen among patients who received study drug as second-line or greater treatment (von Minckwitz et al., 2013; Gradishar et al., 2005). Based on these data, *nab*-paclitaxel 260 mg/m^2 Q3W has obtained regulatory approval for use in MBC in more than 40 countries. In Europe, it is licensed for the treatment of MBC in adults who have failed first-line treatment for metastatic disease and for whom standard anthracycline-containing therapy is not indicated (EMA, 2013).

Since the approval of *nab*-paclitaxel in MBC, data have emerged to suggest that alternative dosing schedules of *nab*-paclitaxel are feasible (Blum et al., 2007; Gradishar et al., 2009, 2012), and that QW dosing may be associated with improved clinical benefits, as was seen with QW dosing of conventional paclitaxel. However, these data have not been confirmed in randomized phase III trials, and there is uncertainty among physicians regarding the optimum dosing schedule to select. Given these challenges, a group of experts convened to review the available evidence and, combined with their clinical experience, compile recommendations to help guide clinicians in selecting the optimum dosing schedule of *nab*-paclitaxel in individual patients with MBC.

2. Methods

2.1. Literature review

A literature search for clinical trial publications and presentations of *nab*-paclitaxel from January 2003 to October 2014 was carried out using PubMed and online search facilities for abstracts