Amelioration of docetaxel/cisplatin induced polyneuropathy by α-lipoic acid

Docetaxel (Taxotere®, Aventis, Strasbourg, France) is currently considered to be one of the most important anticancer drugs. It is a semi-synthetic agent derived from baccatin III extracted from renewable Taxus baccata needles, which binds to tubulin inducing its polymerization [1]. It inhibits cell replication and leads to apoptosis. Docetaxel has displayed significant antitumor activity against non-small-cell lung cancer (NSCLC), head and neck tumors and breast cancer [2].

Apart from myelosuppression (neutropenia), hypersensitivity reactions and fluid retention, one significant adverse reaction associated with the use of docetaxel is a cumulative and predominately sensory neurotoxicity [2]. When combined with other neurotoxic agents, such as cisplatin, this adverse reaction may become dose-limiting. Taxane-induced neuropathy tends to occur early during therapy with amelioration after discontinuation of therapy; whereas, cisplatin-induced neuropathy tends to develop after a critical cumulative dose and frequently worsens during the first months following therapy discontinuation [3].

Alpha-lipoic acid (Thioctacid®; Asta Medica, Frankfurt, Germany), which has been shown to be effective in both the somatic and the autonomic neuropathies in diabetes, normalizes the endoneural bloodflow [4], reduces oxidative stress [5, 6] and improves vascular dysfunction [7]. In a placebo-controlled trial in patients with diabetic neuropathy, a significant relief of neuropathic symptoms was observed in patients who received α-lipoic acid [8].

We investigated the therapeutic potential of α-lipoic acid to counteract docetaxel plus cisplatin related peripheral neuropathy (PNP) in patients with advanced gastric cancer (n = 5), NSCLC (n = 6), and head and neck tumor (n = 3).

From October 2000 to March 2001 a total of 14 patients who received docetaxel 50 mg/m² in combination with cisplatin 50 mg/m² every 2 weeks, experienced at least one symptom of paresthesia, dysesthesia or pain, including a burning sensation, thus fulfilling the criteria of polyneuropathy [9]. Their pretreatment characteristics are summarized in Table 1. Neurological symptoms were serially evaluated in all patients before each cytotoxic drug administration according to the World Health Organization (WHO) grading system, which has been developed to assess the neurotoxicity occurring during treatment with potentially neurotoxic agents [9]. All patients who experienced PNP grade 2 (severe paresthesia and/or mild weakness) or grade 3 (intractable paresthesia and/or marked motor loss) during or after docetaxel/cisplatin combination chemotherapy received α-lipoic acid. The treatment regimen consisted of α-lipoic acid 600 mg i.v. once a week for 3–5 weeks followed by 1800 mg t.d.s. until full recovery from neurological symptoms for a maximum of 6 months. After a median of eight chemotherapy courses (range 6–12) and a median cumulative docetaxel dose of 400 mg/m² (range 300–600 mg/m²) a total of 14 patients suffered from PNP grade 2 (10 patients) or 3 (four patients).

Treatment with α-lipoic acid resulted in an improvement in neurological symptoms (by ≥1 WHO toxicity score) in six patients with grade 2, and two patients who suffered from grade 3 PNP. The median time to response was 4 weeks (range 3–12 weeks) and the median duration of treatment with α-lipoic acid was 2 months (range 1–4 months). Six patients did not respond, two of them initially presented with PNP grade 3, and four had PNP grade 2. Apart from moderate gastric pain in two patients and WHO grade 1 and 2 nausea in one patient each, α-lipoic acid did not cause any other adverse reactions.

Our data suggest that α-lipoic acid administered in the current schedule was able to counteract docetaxel-related PNP. Despite other supportive therapies (such as amifostin, calcium/magnesium infusion, sodium channel blockers and gabapentin), further

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Table 1. Patient characteristics
investigation of α-lipoic acid in the treatment of docetaxel ± cisplatin-related polyneuropathy seems warranted.

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References

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