Gabapentin for Chemo-Induced Peripheral Sensory Neuropathy. A Pilot Study

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INTRODUCTION

Peripheral neuropathy is a major dose-limiting side effect of many chemotherapeutic agents. The type and degree of neuropathy depends on the chemotherapy drug, dose-intensity and cumulative dose. Disabling peripheral neuropathy has a significant negative impact on quality of life which can result in the cessation of treatment in order to prevent irreversible damage to the motorial function of limbs. There are few drugs (GSH, amifostine) that are effective in the prevention of this toxicity, especially for platinum-derivates and a number of other drugs have been used for therapy. However, there is no standard treatment. Over the last few years gabapentin has shown its efficacy for neuropathic pain. The aim of this study was to demonstrate the activity of gabapentin for peripheral sensorial neurotoxicity.

BACKGROUND: Neurotoxicity is a frequent side effect of chemotherapy. There are few drugs (GSH, amifostine) that are effective for the prevention of this toxicity, especially for platinum-derivates and a number of other drugs have been used for therapy. However, there is no standard treatment. Over the last few years gabapentin has shown its efficacy for neuropathic pain. The aim of this study was to demonstrate the activity of gabapentin for peripheral sensorial neurotoxicity.

PATIENTS AND METHODS: 25 patients with peripheral sensorial neurotoxicity equal/over 2 according to the NCI scale and treated with potentially neurotoxic drugs entered the study. Treatment was: gabapentin 400 mg/die for two days, 400 mg bid for a further two days and then 400 mg tid as maintenance. Response was evaluated with a Zero to 10 Numerical Scale before treatment (T0) and after 30 days (T1). The median age was 66 (range 41 - 75); 16 females and 9 males. 10 breast cancer patients, 5 colon cancer patients, 3 lung cancer patients, 2 bladder cancer patients, 1 gastric cancer patient, 1 ovarian cancer patient, 1 melanoma patient, 1 laryngeal cancer patient and 1 oral cavity cancer patient. Previous treatments included: paclitaxel in 6 patients; cisplatin/paclitaxel in 5 patients; oxaliplatin in 5 patients; vinorelbine/oxaliplatin/paclitaxel in 2 patients; docetaxel in 2 patients; vinorelbine/paclitaxel in 1 patient; docetaxel/vinorelbine/oxaliplatin in 1 patient; cisplatin/oxaliplatin in 1 patient; vinorelbine in 1 patient and cisplatin in 1 patient.

RESULTS: 19 patients were eligible for evaluation response. 11 out of 19 (60%) patients responded with an improvement of sensorial neurotoxicity, documented by a median reduction of 3 points in numerical scale (range 1 - 5). The main toxicity was lethargy for 8 patients (32%); and for 5 this was associated with mental clouding. 1 patient reported agitation.

CONCLUSIONS: Our study seems to provide evidence that gabapentin is a promising drug for sensorial neurotoxicity induced by chemotherapy, although it requires further investigation in a randomised phase III study.

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Key words: Gabapentin, Neurotoxicity, Chemotherapy

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Another study demonstrated the effect of gabapentin for neuropathic pain caused by anticancer treatments [10]. In this trial peripheral neurological injury caused by surgery, radiotherapy or chemotherapy was evaluated but there have been no controlled studies regarding the use of gabapentin in patients with chemo-induced neurotoxicity. Therefore it was decided to carry out a phase II study in order to assess the activity and the side effects of gabapentin in patients with chemo-induced peripheral sensory neuropathy.

**Patients and Methods**

**Eligibility Criteria**

All consecutive patients with solid tumors and chemotherapy-induced neurotoxicity entered the study. Other selection criteria included: (a) previous treatment with potentially neurotoxic drugs (cisplatin, paclitaxel, docetaxel, vinorelbine, oxaliplatin), where treatment had been completed no more than 60 days prior to the study (b) peripheral sensory neuropathy equal/over 2 according to the NCI (identified as equal/over 4 on the 0 to 10 Numerical Scale (c) first occurrence of neurotoxicity (d) ECOG: 0-2 (e) normal mental status, defined as the absence of clinical confusion, memory or concentration deficit (f) at least 18 years old. Patients with neurotoxicity associated with direct tumor involvement, diabetic or other neuropathy (vascular, alcoholic) and brain metastases were excluded. Previous treatment with gabapentin or current treatment with anticonvulsants, antidepressants and analgesics was not permitted. An informed verbal consent was obtained from all patients.

The pre-treatment evaluation included: a complete medical history (to document the previous treatment with neurotoxic drug); a physical examination and the compilation of a Numerical Scale (T0).

**Study Design**

Gabapentin was administered orally: 400 mg/die for the first two days, 400 mg bid for a further two days and then 400 mg tid as maintenance. Neurotoxicity was measured using a Numerical Scale (0 no symptoms; 10 worst paresthesias imaginable), that was recorded prior to the treatment commencement (T0) and then 30 days after the completion of treatment (T1). Patients with recorded improvement of paresthesias, documented by a Numeric Scale reduction were considered as "responders". In accordance with the t-student test, with a median Numeric Scale value of 7 on T0 and with the aim of a median reduction of 2 points on T1, the number of patients required was 15 (alpha error 0.05 with a power of 80%).

**Results**

Twenty-five patients with advanced cancer who had undergone previous treatment with neurotoxic drugs entered the study. 16 females and 9 males; 15 with NCI gr 3 and 10 with gr. 2 sensory neuropathy. (10 breast cancer, 5 colon cancer, 3 lung cancer, 2 bladder cancer, 1 gastric cancer, 1 ovarian cancer, 1 melanoma, 1 laryngeal cancer, and 1 oral cavity cancer).

Nineteen out of 25 patients (76%) were eligible for evaluation and all for toxicity. 1 patient died before evaluation, 4 patients refused to continue gabapentin administration and 1 patient dropped out the study due to side effects (Table 1).

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
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<tr>
<td>N° patients</td>
<td>25</td>
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<td>Evaluable patients</td>
<td>19 (76%)</td>
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<tr>
<td>Median age</td>
<td>66 (range 41-75)</td>
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<tr>
<td>Female</td>
<td>16</td>
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<td>Male</td>
<td>9</td>
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<td>Type of cancers</td>
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<td>Breast cancer</td>
<td>10</td>
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Eleven of the 19 eligible patients responded (60%) with an improvement of sensorial neurotoxicity, documented by a median reduction of 3 points in Numerical Scale (range 1 - 5), beginning from a median of 7 points. When used with intention-to-treat, the success rate of gabapentin was 44% (11 out 25 patients). Toxicity was as follows: the main side effect was lethargy in 8 patients (32%); and for 5 this was associated with mental clouding (20%) 1 patient reported severe memory deficit with mental clouding and another patient reported agitation (Table 2).
16 patients (64%) completed the study with the planned gabapentin dose of 1200 mg/die; only 1 patient reached the dose of 2400 mg/die, without side effects. 2 patients took the drug for more than 1 year and are still undergoing treatment.

CONCLUSIONS

Gabapentin is a new anticonvulsant with established efficacy in non malignant neuropathic syndromes [11]. Furthermore, data from placebo-controlled trials confirmed its efficacy as an adjuvant drug for neuropathic pain [7, 8] and for neuropathic cancer pain [12], at doses of 1800 to 3600 mg/daily.

The exact mechanism of gabapentin’s analgesic action is unknown. Recent data suggests that the drug binds to the specific gabapentin protein found in the brain and spinal cord, which is a sub-unit of voltage-gated neuronal calcium channels [13]. Gabapentin also exerts an indirect effect on the voltage dependent sodium channels, slightly inhibits glutamate and reduces the excretion of certain neurotransmitters, such as serotonin, dopamine and noradrenaline [14].

In this study gabapentin was only administered to patients with chemo-induced peripheral sensory neuropathy. As far as is known, this is one of the few trials that planned to test gabapentin activity in these patients [10].

The results of the study documented an improvement of paresthesias for 11 out of 25 patients (60%) with an intention-to-treat percentage of 44% (11/25). This data overlaps with that obtained by Bosnjak et al; where 11 out of 23 (48%) patients responded to gabapentin administration with a reduction in pain intensity, at the doses of 900-1200 mg/daily. (the same doses used in this study).

However, in the Bosnjak trial only 7 patients experienced pain induced by chemotherapy and it is unclear whether or not these patients were included as "responders". Other preliminary data with gabapentin has shown encouraging results and seems to confirm the activity of this drug [3]. In the Mariani et al trial, gabapentin was administered for neuropatic symptoms induced by oxaliplatin-based chemotherapy; in seven patients neuropathy disappeared and did not reoccur with subsequent chemotherapy treatments.

The toxicity profile of gabapentin was acceptable and lethargy was the main toxicity (32%). However, 4 patients refused to continue gabapentin administration due to mental clouding (1 patient dropped out of the study for the same side effect) and only 16 patients (64%) reached the planned gabapentin dose of 1200 mg/die.

Gabapentin side effects were higher than expected but it should be considered that all patients had metastatic cancers (9 with 2 metastatic sites) and their tolerance to gabapentin could have been reduced (also by concomitant medications).

Obviously, the results of this study should not be considered as anything other than preliminary due to the number of patients (although statistically correct) and the fact that it is a single-center, uncontrolled and open study.

However, it is believed that this study appears to show that gabapentin may be an option for the treatment of chemo-induced neurotoxicity.

This important side effect is very disabling and often induces the oncologist to discontinue an active treatment in order to avoid irreversible damage to limb function.

The use of an active drug may overcome neurotoxicity and may enable the continuation of chemotherapy cycles.

REFERENCES


