Clinical Research Paper

Prophylactic effect of amifostine on oxaliplatin-related neurotoxicity in patients with digestive tract tumors

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Background and Objective: Oxaliplatin, an active agent used widely in treating digestive tract tumors, displays a frequent dose-limiting neurotoxicity. This study was to assess the clinical efficacy of amifostine in preventing neurotoxicity induced by oxaliplatin.

Methods: A total of 92 patients with colorectal cancer or gastric cancer were enrolled, and randomly assigned to receive amifostine (500 mg/m²) (amifostine group, 46 patients) or glutamine (1500 mg/m²) (control group, 46 patients) just before oxaliplatin infusion. All patients received FOLFOX4 regimen. Neurological toxicity and efficacy of chemotherapy were assessed. Results: The occurrence rates of grade I–II and grade III–IV peripheral neurotoxicity after chemotherapy were significantly lower in amifostine group than in control group (10.9% vs. 73.9%, p < 0.001; 2.2% vs. 19.6%, p = 0.007). The frequency of regimen change because of chemotherapy-related neurotoxicity was significantly lower in amifostine group than in control group (4.3% vs. 23.9%, p = 0.007). The overall response rates of evaluable patients were 44.4% in amifostine group and 38.5% in control group (p = 0.66).

Conclusion: Amifostine could significantly reduce the incidence and severity of peripheral neurotoxicity caused by oxaliplatin in the patients with digestive tract tumors, but not affect response to chemotherapy.

Oxaliplatin is a widely used high performance broad-spectrum platinum preparation of the third generation. It has no renal toxicity, and its gastrointestinal reaction and bone marrow toxicity are mild. It has no cross resistance with other platinum preparations. It plays an important role in the treatment of digestive tract tumors, especially metastatic colorectal carcinoma. Oxaliplatin displays a frequent neurotoxicity with an occurrence rate of 85–100%, limiting its clinical application and efficacy improvement. Reduced glutathione and calcium-magnesium preparation are commonly used prophylactic drugs. However, their efficacy is not satisfying. Currently, there is no ideal prophylactic treatment for oxaliplatin-related neurotoxicity.

Amifostine, a broad-spectrum cytoprotection agent, can alleviate renal toxicity, hematotoxicity and mucosal toxicity induced by chemotherapy with platinum, and it may alleviate neurotoxicity of cisplatin and carboplatin with no weakening in their efficacy. However, its effect on neurotoxicity related with oxaliplatin is still unclear. In order to determine the effect of amifostine on oxaliplatin-induced neurotoxicity and its clinical application, we treated digestive tract tumor patients with prophylactic administration of amifostine before oxaliplatin chemotherapy from January, 2006 to December, 2007. The results are reported as below.

Patients and Methods

Patients’ data. Ninety-two patients with pathologically confirmed advanced or relapsed colorectal carcinoma or gastric carcinoma were recruited. Inclusive criteria were as follows: (1) receiving chemotherapy containing oxaliplatin, (2) receiving chemotherapy for the first time, (3) with ECOG score of 0–2, (4) without contraindication to chemotherapy. Exclusive criteria were as follows: (1) nervous system diseases including nervous system cancerous metastasis, (2) diabetes, (3) alcohol-related diseases. The patients were assigned into amifostine group and control group by random number table method. Informed consent was signed before treatment. Patient information is shown in Table 1. There was no significant difference in clinical features between these two groups.

Treatment schedule. All patients were treated with FOLFOX 4 regimen: 2-hour intravenous infusion of oxaliplatin (85 mg/m²) on Day 1, 2-hour intravenous infusion of calcium folinate (200 mg/m²) on Day 1 and Day 2, intravenous injection of 5-fluourouracil (DDP, 400 mg/m²) and 22-hour intravenous infusion of DDP (600 mg/m²) on Day 1 and Day 2. The above procedure was repeated every two weeks; four weeks as a cycle to a total of 6 cycles. Chemotherapy was terminated when tumor progressed (refer to Recist standard). For amifostine group, 500 mg/m² amifostine (AMF, Sun Pharmaceutical, India) was added into 50 mL of normal saline and administered by intravenous infusion for 15 min, intravenous infusion of oxaliplatin was started within 30 min after the completion of amifostine administration; 10 mg dexamethasone and 5 mg tropisetron were administered by intravenous injection before...
amifostine administration. For control group, 1500 mg/m² reduced glutathione, instead of amifostine, was administered. Calcium-magnesium preparation was not used in either group. Toxicity was treated by the same standard. For grade III–IV toxicity, the dose was adjusted and returned to the original one only when toxicity was decreased to below grade II. For grade IV non-neurotoxicity, the doses of all drugs for the next cycle were decreased by 25%. For grade III–IV neurotoxicity, the dose of oxaliplatin was decreased by 25%. Chemotherapy would be terminated when two successive grade IV toxicities occurred.

Assessment of efficacy and toxicity. According to NCI-CTC 2.0 standard, chemotherapy-related toxicity was assessed in every cycle, while neurotoxicity was assessed before the first chemotherapy and at the end of cycles two, four and six. Short-term efficacy was assessed according to Recist standard (in 2000).

Statistical analysis. Statistical analysis was performed by Fisher exact test and \( \chi^2 \) test using SAS 9.0 software. \( \alpha \leq 0.05 \) was considered as significant.

Results

A total of 92 patients were included. Ninety patients completed four cycles of chemotherapy and 87 of them completed six cycles. Toxicity was assessable in all patients. Short-term efficacy was assessable in 53 patients with foci.

Neurotoxicity. The occurrence rates of grade I–II and grade III–IV neurotoxicity were significantly lower in amifostine group than in control group (10.9% vs. 73.9% for grade I–II, 2.2% vs. 19.6% for grade III–IV, \( p < 0.001 \)). The occurrence rate of temporal acute neurotoxicity was significantly lower in amifostine group than in control group (6.5% vs. 95.7%, \( p < 0.001 \)). The occurrence data of neurotoxicity assessed every two weeks are shown in Table 1. The occurrence rate of grade I–II neurotoxicity in amifostine group was always significantly lower than that in control group. The occurrence rate of grade III–IV neurotoxicity in amifostine group was also lower than that in control group, especially at the end of cycle six (\( p = 0.006 \)).

Change of chemotherapy schedule and short-term efficacy. In amifostine group, one patient withdrew after cycle two and one withdrew after cycle five for economic reason; one withdrew after cycle four because of tumor progression; the dose of chemotherapy was decreased in one patient due to oxaliplatin-related grade III toxicity; chemotherapy was delayed in one patient due to grade III anemia. In control group, one patient withdrew during cycle two and two withdrew during cycle four for tumor progression; the dose of oxaliplatin was decreased and chemotherapy was delayed in seven patients because of neurotoxicity; two withdrew during cycle five because of neurotoxicity; chemotherapy was delayed in two patients because of non-neurotoxicity. The proportion of chemotherapy schedule adjustment due to toxicity was significantly lower in amifostine group than in control group (4.3% vs. 23.9%, \( p = 0.007 \)).

The short-term efficacy was assessable in 27 patients in amifostine group and in 26 patients in control group (Table 3). The response rates were 44.4% in amifostine group and 38.5% in control group (\( p = 0.659 \)); the benefit rates were 96.3% in amifostine group and 88.5% in control group (\( p = 0.291 \)).

Other chemotherapy-related toxicities. For grade III–IV hematotoxicity, the occurrence rates of hypoleukemia were 8.7%
in amifostine group and 17.4% in control group (p = 0.216), those of thrombocytopenia were 2.2% in amifostine group and 6.5% in control group (p = 0.617), and those of anemia were 2.2% in amifostine group and 6.5% in control group (p = 0.617).

The occurrence rates of grade I–II nausea and vomiting were 52.2% in amifostine group and 50.0% in control group (p = 0.835); those of grade III–IV nausea and vomiting were 2.2% in amifostine group and 6.5% in control group (p = 0.617).

Slight elevation of transaminase was found in two patients in control group. There was no abnormality of renal function in both groups.

In amifostine group, gradual decrease of blood pressure was found in four patients when amifostine infusion was almost finished. Their blood pressure recovered soon (3–5 min) after prostration and rapid infusion of normal saline. No other special treatment was needed, therefore, no patients discontinued treatment. Hypotension would occur during the next infusion with no aggravation. This phenomenon was not found in control group.

Discussion

Oxaliplatin, with similar chemical structure and function mechanism as cisplatin and carboptatin, inhibits tumor proliferation through binding with DNA, blocking DNA replication and transcription to inhibition. However, its neurotoxicity is more frequent and unique, and it can produce obvious neurotoxicity with a concentration in nervous tissue far lower than those of other platinum preparations. Its neurotoxicity is characterized by accumulative dose-dependent chronic nervous system symptoms and accumulative dose-independent acute nervous system symptoms. The mechanism of oxaliplatin-induced chronic neurotoxicity is similar with that of other platinum preparations, which is related with drug accumulation in peripheral nerve, especially in the posterior root ganglion, that causes DNA interference and damage with morphologically visible karyopyknosis and axonal degeneration. Platinum preparations induce an increasing production of free radicals including active oxygen, superoxide anion and hydroxyl, which results in DNA fragmentation. This is also an important factor for its neurotoxicity. Reduced glutathione has prophylactic and therapeutic effect on neurotoxicity induced by cisplatin, carboplatin and oxaliplatin, which is mainly attributed to its free radical scavenging ability. Although it is widely used in clinic, the effect is not satisfying.

Amifostine, a thiophosphate pan-cytotoxoprotection reagent, can release active sulphhydril with the help of alkaline phosphatase. It has stronger free radical scavenging and antioxidative ability than reduced glutathione. Furthermore, it can bind with cytotoxic drugs to block formation of DNA adduct with chemotherapeutics, thereby accelerating repair of damaged DNA. Previous studies indicated that amifostine had prophylactic effect on neurotoxicity induced by cisplatin and paclitaxel via opposing damage to neuron axon as well promoting growth and repair. However, there are only a few studies about the effect of amifostine on oxaliplatin-induced neurotoxicity and the results are unclear.

Penz et al. had treated 15 colorectal carcinoma patients who had already developed grade II–III oxaliplatin-induced neurotoxicity with subcutaneous injection of low dose amifostine before the next administration of oxaliplatin. The symptoms were attenuated or disappeared in ten patients, suggesting that amifostine can decrease oxaliplatin-induced neurotoxicity. Our results are consistent with theirs, in that the occurrence rates of both mild and severe neurotoxicity in amifostine group were significantly lowered. In our study, the protective effect of amifostine on the nervous system was manifested from the very beginning, which contributed to decreased occurrence of mild toxicity; with the progression of treatment, the occurrence rate and severity of neurotoxicity increased, and the prophylactic effect of amifostine on severe neurotoxicity became obvious; at the end of treatment, the occurrence rate of severe neurotoxicity in amifostine group had been significantly lowered than that in glutathione group, suggesting the inhibitory effect of amifostine on cumulative toxicity.

It is noteworthy that amifostine has significant prophylactic effect on acute neurotoxicity. In our study, cold air or cold object-induced electric shock-like indisposition, such as acmesthesia and numbness, was found in 95.7% of the patients in control group although they had received prophylactic administration of glutathione; while only 6.5% of the patients in amifostine group felt mild indisposition, and their lives were not influenced expect for being deprived of cold water and cold food on the day of chemotherapy. Acute neurotoxicity is limited to oxaliplatin, which is attributed to delayed inactivation of voltage-gated Na+ channel on the membrane of myelinated afferent fibers by oxalic ions released from oxaliplatin. However, it can not explain why motor neuron is involved. Although intravenous injection of oxalic ion chelators, such as calcium gluconate and magnesium sulfate, can decrease the occurrence and severity of acute neurotoxicity, there were still 20% patients showing symptoms and 4% patients withdrawing because of acute neurotoxicity. Blockage of Na+ channel with carbamazepine didn't show reliable prophylactic effect. The mechanism of oxaliplatin-induced acute neurotoxicity is not completely clear. In addition, the prophylactic effect of amifostine on oxaliplatin-induced acute neurotoxicity is unclear and thus need further investigation.

Hematotoxicity and other toxicities were not our focal points. In our study, there was no significant difference in gastrointestinal reaction and grade III–IV hematotoxicity between amifostine group and control group, no protective effect of amifostine on corresponding tissues was observed. Nausea, vomiting and hypotension are common adverse effects of amifostine, which may account for increased occurrence of mild nausea and vomiting in our study. Hypotension usually occurred at 12–15 min after the beginning of amifostine infusion, which can be controlled by assessment and correction of potential hypovolemia on the day before, rapid infusion of dexamethasone and normal saline, limiting infusion duration of amifostine, and maintenance of prostration during amifostine infusion. No severe hypotension occurred in our study. As for mild hypotension, the duration was short and it was recovered soon.

We did not perform survival analysis due to short observation duration. However, the complication rate of chemotherapy as scheduled was higher in amifostine group, while the withdrawal rate due to toxicity was lower in amifostine group as compared with control group. The short-term outcomes were also better in amifostine group than in control group. The results are consistent with related meta-analysis, indicating that amifostine do not decrease the antitumor effect of chemotherapeutics.

In summary, our results support that prophylactic administration of amifostine can alleviated oxaliplatin-induced neurotoxicity.
Prophylactic effect of amifostine on oxaliplatin-related neurotoxicity in patients with digestive tract tumors and can be used in combined chemotherapy of oxaliplatin, calcium folinate and fluorouracil both effectively and safely.

References