Pharmacological Reports
2006, 58, 30–34
ISSN 1734-1140

Copyright © 2006
by Institute of Pharmacology
Polish Academy of Sciences

Cytoprotective effect of amifostine in the treatment of childhood neoplastic diseases – a clinical study including the pharmacoeconomic analysis

Małgorzata Stolarska, Wojciech Mlynarski, Beata Zalewska-Szewczyk, Jerzy Bodalski

Oncohaematology Unit, Department of Pediatrics, Medical University of Łódź, Sporna 36/50 91-738 Łódź, Poland

Correspondence: Malgorzata Stolarska, e-mail: m.stolarska@wp.pl

Abstract:
Amifostine is an active aminothiol, which has unique properties as a radio- and chemoprotective agent. It has been reported to prevent myelosuppresion and reduce the toxic effects of intensive cancer treatment.
In the study, 57 courses of chemotherapy in 18 children treated because of neoplastic disease were analyzed to assess the early side effects induced by cytotoxic anticancer therapy. In 18 of them amifostine was used as the cytoprotective agent. The estimation of adverse effects was made in accordance to WHO scale of toxicity, and the pharmacoeconomic analysis was based on the costs of intravenous antibiotics, G-CSF, GM-CSF, blood preparations, immunoglobulines and days of hospitalization.
The amifostine use in supportive therapy of neoplastic diseases in children decreases the number of infections thanks to the diminishing of myelotoxic effect. This not only improves the comfort of the patient but also shortens the time of hospitalization. The amifostine therapy limits the costs of treatment, but high price of the drug itself, makes however, the chemotherapy with cytoprotection comparable in pharmacoeconomic analysis to the standard treatment.

Key words:
amifostine, neoplastic diseases, children, cytoprotection

Introduction

Cytoprotection is one of the ways to improve the results of cytotoxic, anticancer therapy. Over the last few years, the amifostine has rested in the interest because of its unique properties as a radio- and chemoprotective agent. Amifostine is an analogue of cysteamine – the aminothiol (WR 2721). At the tissue site, this pro-drug is dephosphorylated by membrane-bound alkaline phosphatases to its active metabolite – the free thiol (WR 1065). This form of the drug can penetrate the cell membrane by passive or active mechanism. Its concentration is very high in normal tissues. This selective uptake of amifostine is due to the high activity of membrane phosphatases in normal cells comparing to cancer ones. Therefore, the drug can prevent the cells from radio- or chemotherapy-induced adverse effects [6, 10].

The mechanisms of action of amifostine are still not well known. There are evidences that WR 1065 is a potent scavenger of reactive oxygen species and can reduce the DNA-damage caused by free radicals. It also protects the DNA against the toxicity of platinum drugs and inhibits the membrane transport of antracyclins. It was discovered that amifostine stimulates the

formation of multipotent and erythroid bone marrow progenitors [6, 10, 21].

Recent studies show that the active thiol is able to act in more specific ways. For example, it can influence the formation and accumulation of protein p53 [17, 18] and catalytic inhibition of DNA topoisomerase II – (topo II)alpha, which prolongs the cell cycle and gives more time for DNA repairs [20, 21]. Besides, amifostine with carboplatin may additively act as a pro-apoptotic factor on the leukemic cells [16].

Due to these mechanisms amifostine has been reported to prevent myelosuppression, to reduce nephro- neuro- and ototoxic effects of cytotoxic therapy, to diminish the mucosal damage in the gastrointestinal tract and genitourinary system and even to protect against the mutagenic effects of cancer treatment [5, 7, 9, 10, 20].

The aim of the study was to assess the early side effects induced by cytotoxic, anticancer therapy and to analyze cost effectiveness of this therapy in children treated because of solid tumors and acute nonlymphoblastic leukemias (ANLL) with or without amifostine as a cytoprotector.

Materials and Methods

The study included the retrospective analyses of 57 courses of chemotherapy in 18 children treated because of solid tumors and ANLL in the Department of Paediatrics, University of Medicine in Łódź years 1998–2001 .

Eighteen courses included amifostine as cytoprotector (the group A). Every course was compared with at least two similar courses given without amifostine (the group C).

The mean age of the patients was 7.1 ± 1.9 years. There were 13 girls and 5 boys.

Amifostine (Ethyol) was provided by Schering-Plough.

The drug was administered as a short intravenous infusion before alkylating agents (cyclophophamide, ifosphamide), carboplatin and/or anthracyclins. The dose was 910 mg/m^2.

The estimation of early adverse effects of the treatment was made in accordance to the four degrees WHO scale of toxicity including particularly such elements as:

- mean degree of myelotoxicity
- duration of thrombocytopenia
- number of blood transfusions
- duration of neutropenia and the use of colony stimulating factors – G-CSF and GM-CSF
- severity of infectious complications
- necessary period of hospitalization
- degree of emetogenity

The pharmacoeconomic analysis was based on the costs of:

- intravenous antibiotics
- G-CSF and GM-CSF
- blood preparations
- immunoglobulins
- days of hospitalization

Significance of differences between groups was estimated by the Mann-Whitney's and Wilcoxon's tests. The level of significance (p) was considered significant if < 0.05.

Results

The mean degree of myelotoxicity was lower in the group A (2.54) but the difference was not statistically significant comparing to the group C (2.71).

The mean duration of neutropenia in the group A was 6.5 days and the children needed to receive G-CSF during 4.1 days. In the group C, the time of neutropenia was a little longer – 6.8 days and the time of G-CSF administration was 5.7 days. The differences were not statistically significant (Fig. 1).

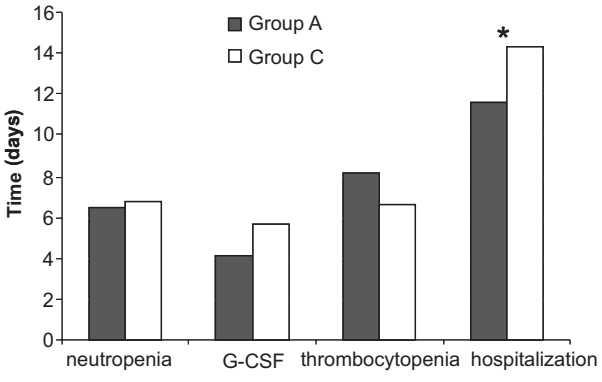

Fig. 1. Mean duration of neutropenia, thrombocytopenia, colony stimulating factors (G-CSF) treatment and hospitalization in amifostine-treated (**A**) and non-treated group (**C**), * – statistical significance ($p < 0.05$)

The patients from the group A required less erythrocyte transfusions (0.8 *vs*. 1.1)

In the group A the thrombocytopenias were more severe, lasted longer (8.2 days *vs*. 6.6 days) and the children required, on the average 1.5 platelet transfusions per course of chemotherapy (in the group C – 0.5 platelets transfusions) But all these results are not statistically significant (Fig. 2).

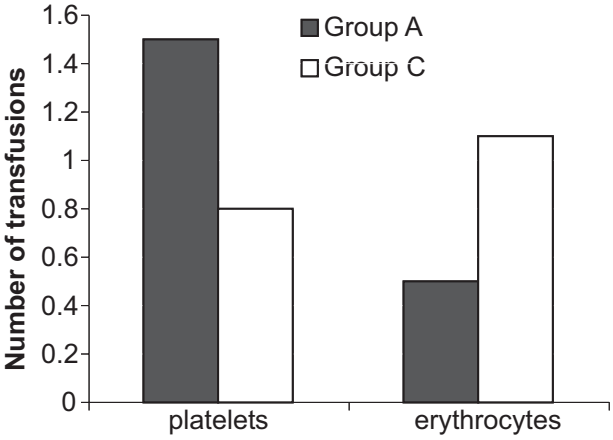

Fig. 2. Mean number of platelet and erythrocyte transfusions in amifostine-treated (**A**) and non-treated group (**C**)

In spite of neutropenia in the group A, the severity of infectious complications was significantly lower than in the group C (0.72 *vs*. 1.02 degrees according to WHO scale) p = 0.049. This influenced the duration of hospitalization which lasted on the average 11.6 days in the group A and 14.3 days in the group C (p = 0.049) (see also Fig. 1).

The chemotherapy with amifostine induced more vomiting. The emetogenity in the group A was estimated at 1.55 degree according to WHO scale comparing to 0.64 in the group C (no statistical significance).

The costs of therapy were determined, first of all, by the differences in antibiotic therapy between the group A and C. The costs of other elements taken into consideration like the blood preparations, the immunoglobulins and even G-CSF, GM-CSF are similar in both groups and not significantly lower in the group A. The mean cost of intravenous antibiotics in one course of chemotherapy with amifostine was 242 PLN, and without the cytoprotectant – 896 PLN (p = 0.037). In the group C, the costs of antibiotics made 9.9% of

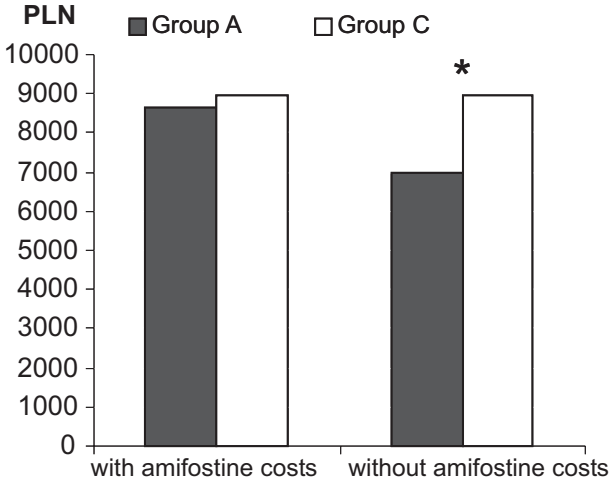

Fig. 3. Mean cost of one course of chemotherapy with and without costs of cytoprotectant in amifostine-treated (**A**) and non-treated group (**C**), * – statistical significance (p < 0.05)

total costs of therapy, and in the group A, this percentage was only 3.6.

The calculation of total costs showed, that the mean cost of one course of chemotherapy with amifostine is significantly lower (7000 PLN) than without it (8977 PLN). But the difference is visible only when the cost of amifostine itself is excluded (p = 0.048). When the cost of Ethyol is added to the others, the total costs of one course in the group A and C are nearly the same (8650 PLN *vs*. 8977 PLN, p = NS) (Fig. 3).

Discussion

Cytotoxicity of antineoplastic therapy often makes it impossible to cure the patient. Dose-limiting toxicity, which can impact the efficacy of the treatment, is due to the inability of drugs to differentiate between normal and malignant cells. Chemoprotectants have been developed as a method to limit the toxicity of antineoplastic agents by providing site-specific protection for normal tissues without compromising antitumour efficacy. The thiol group donors seem to be one of the most promising lines of cytoprotection. That is why amifostine is in the center of interest. [3, 12].

The amifostine was used first of all in adults treated because of head and neck cancers, lung, breast cancers and other malignancies, but it can be equally effective in children [3, 11, 15].

The activity of amifostine protects first of all from cisplatin-related neurotoxicity and nephrotoxicity, cardiac toxicity due to anthracycline treatment and myelotoxicity secondary to alkylating agents and carboplatin therapy [12].

In our study we didn't notice particular nephro-, neuro- or cardiac toxicity after analyzed courses of chemotherapy in both A and C groups. These kinds of toxicities are difficult to estimate after a single application of cytotoxic drugs. They usually accelerate whole anticancer therapy and can be symptomatic after many months of treatment.

Myelotoxicity appears in several days after chemotherapy and influences strongly the course of the disease. Analyzing the courses of chemotherapy with amifostine (the group A) we observed the tendency to better hematologic recovery, comparing to the group without the drug (C), even when the differences were not statistically significant. The duration of neutropenia was shorter, the reaction to colony stimulating agents (G-CSF, GM-CSF) was better, and the number of necessary blood transfusions was smaller. Lower myelotoxicity in the group A results in diminishing the severity of all kinds of infections accompanying neutropenia. This shortens the duration of hospitalization, improves the quality of life and makes the anticancer therapy safer. There are some studies in the literature, mostly randomized, where the authors observed significantly better hematologic recovery and less infectious complications, mucositis, diarrhoea, fever etc. in the group of patients pretreated with amifostine. The authors emphasize both clinical and economical benefits of using amifostine in supportive care [1, 2, 8]. There are evidences (*in vitro*) that amifostine is not only the protectant of the bone marrow stem cells but also can stimulate their formation and differentiation [13]. In other studies, the opinions about efficacy of amifostine are more cautious. The authors indicate better tolerance of chemotherapy due to small number of side effects, but without significant differences in duration of neutropenia, severity of trombocytopenia, duration of antibiotic therapy and hospitalization. [9, 19].

It is impossible not to notice that in the group A, the episodes of trombocytopenia were more severe and lasted longer. The children needed more platelet transfusions than in the group C. This could have been accidental and due to not randomized study. The difference was not statistically significant.

The safety of the patient and quality of life is very important in the treatment of the child suffering from neoplastic disease, but nowadays we must also consider the problem of cytoprotection from the economic point of view. The pharmacoeconomic analyses usually show a lot of benefits from using amifostine in supportive care [2, 4, 9, 14]. In our study the low costs of antibiotics used in the group A diminished significantly the costs of whole therapy. But unfortunately this difference was visible only when the cost of amifostine was excluded. Inclusion of amifostine in the costs calculation abregated the difference. It is important to remember that we investigated only the early side effects of chemotherapy. We did not take into consideration a protection against nephrotoxicity, neurotoxicity, hepatotoxicity etc. Total cost – efficiency calculation can be notably influenced by the treatment of the late side effects.

Amifostine is well tolerated by children. We did not observe hypotension during infusions of the drug. The only side effects were nausea and vomiting in several cases, well controlled by standard antiemetic treatment.

The amifostine seems to be useful cytoprotectant in chemotherapy in children. There are no evidences that it can influence the antitumor efficacy of cytotoxic drugs. However, confirmation of its clinical and economic benefit, still needs more studies in larger, randomized groups of children.

1. Amifostine use in supportive care of neoplastic diseases in children decreases the number of infectious complications, which can be related to the diminishing of myelotoxic effect of cytotoxic agents and shortens the time of hospitalization.
2. Amifostine use during chemotherapy in children limits the costs of treatment first of all by diminishing the costs of antibiotics. High prize of amifostine itself makes, however, the chemotherapy with cytoprotection comparable in pharmacoeconomic analysis to the standard treatment.

Acknowledgment:
The study was supported by AM No 502-11-838 grant.

References:

1. Awasty BS, Julka PK, Agarwal S, Nair O, Bhamrah R, Rath GK: Effect of amifostine on toxicities associated

with salvage combination chemotherapy. J Assoc Physicians, India, 2001, 49236–49239.
2. Bennett CL, Lane D, Stinson T, Glatzel M, Buntzel J: Economic analyses of amifostine as adjunctive support for patients with advanced head and neck cancer: preliminary resultes from a randomized phase II clinical trial from Germany. Cancer Invest, 2001, 19, 107–113.
3. Bukowski R: Cytoprotection in the treatment of pediatric cancer: review of current strategies in adults and their application to children. Med Pediatr Oncol, 1999, 32, 124–134.
4. Calhoun EA, Bennet CL: Pharmacoeconomics of amifostine in ovarian cancer. Semin Oncol, 1999, 26 Suppl 7, 102–107.
5. Capelli D, Santini G, De-Souza, Poloni A, Marino G: Amifostine can reduce mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cell autotransplant: a retrospective study. Br J Haematol, 2000, 110, 300–307.
6. Capizzi RL: Amifostine: The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapy. Semin Oncol, 1996, 23, Suppl 8, 2–17.
7. Capizzi RL, Oster W: Chemoprotective and radioprotective effects of amifostine: an update of clinical trials. Int J Hematol, 2000, 72, 425–435.
8. Hartmann JT, von-Vangerow A, Fels LM, Knop S, Stolte H, Kanz L, Bokemeyer C: A randomized trial of amifostine in patients with high doses VIC chemotherapy plus autologous blood stem cell transplantation. Br J Cancer, 2001, 84, 313–320.
9. Johnson P, Muers MF, Peake MD, Poulter KM, Gurney EM, Napp VV, Hepburn PM Brown JM: A randomized trial of amifostine as a cytoprotective agent in patients receiving chemotherapy for small cell lung cancer. Br J Cancer, 2001, 84, 19–24.
10. Juszczyński P, Korycka A, Robak T: Clinical pharmacology of amifostine (Polish). Acta Haematol Pol, 1997, 28, 2.
11. Korzon M, Popadiuk S, Plata-Nazar K, Gołębiewski J, Szarszewski A, Czauderna P, Stoba C: Ethyol (Amifostine) – an attempt to use this drug in pediatric oncology. (Polish) Wiad Lek, 1998, 51, Suppl, 4215–4219.
12. Links M, Lewis C: Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. Drugs, 1999, 57, 293–308.
13. List AF, Heaton R, Glinsmann-Gibson B, Capizzi RL: Amifostine stimulates formation of multipotent and erythroid bone marrow progenitors. Leukemia, 1998, 12, 1590–1602.
14. Longo CJ: Choices of methodology in pharmacoeconomics studies. Med Care, 1999, 37, Suppl, AS32–35.
15. Matysiak M, Stańczak E, Wojtowicz A: Amifostine (Ethyol) In supportive therapy of children suffering from acute lymphoblastic leukemia. (Polish) Wiad Lek, 1998, 52 Suppl, 4210–4214.
16. Mirowski M, Rozalski M, Krajewska U, Balcerczak E, Mlynarski W, Wierzbicki R. Induction of caspase 3 and modulation of some apoptotic genes in human acute promyelocytic leukemia HL-60 cells by carboplatin with amifostine. Pol J Pharmacol, 2003, 55, 227–34.
17. North S, El-Ghissassi F, Pluquet O, Verhaegh G, Hainaut P: The cytoprotective aminothiol WR 1065 activates p21 waf 1 and downregulates cell cycle progression through a p53-dependent pathway. Oncogene, 2000, 19, 1206–1214.
18. Provinciali M, Ciavattini A, Di Stefano G, Argentati K, Garzetti G: *In vivo* amifostine (WR 2721) prevents chemotherapy induced apoptosis of peripheral blood lymphocytes from cancer patients. Life Sci, 1999, 64, 1525–1532.
19. Renne S, Krumpelmann S, Bruchelt G, Wiesinger H, Niethammer D, Klingebiel T: Effect of amifostine on neuroblastoma during high dose chemotherapy: *in vivo* and *in vitro* investigations. Anticancer Res, 2000, 20, 4531–4538.
20. Santini V: Amifostine: chemotherapeutic and radiotherapeutic protective effects. Expert Opin Pharmacother, 2001, 2, 479 – 489.
21. Snyder RD, Grdina DJ: Further evidences that the radioprotective aminothiol WR-1065 catalytically inactivates mammalian topoisomerase II. Cancer Res, 2000, 60, 1186–1188.

Received:
February 1, 2005; in revised form: December 2, 2005.