Cancer Chemother Pharmacol (2003) 52: 223–228
DOI 10.1007/s00280-003-0654-4

ORIGINAL ARTICLE

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Amifostine does not reduce the toxicity of the fludarabine and cyclophosphamide regimen in patients with chronic lymphocytic leukemia

Received: 26 December 2002 / Accepted: 29 April 2003 / Published online: 3 June 2003

Abstract *Purpose*: Amifostine is an organic thiophosphate that may selectively protect normal tissues from the toxicities of chemotherapy. The combination of fludarabine and cyclophosphamide (FC) is highly active in patients with chronic lymphocytic leukemia (CLL). Infection is a serious toxicity of the FC regimen. *Methods*: Amifostine was added to the FC regimen in a phase II study of 46 patients with CLL. Patients received FCA (fludarabine 30 mg/m^2 i.v. daily for 3 days, cyclophosphamide 300 mg/m^2 i.v. daily for 3 days, and amifostine 500 mg i.v. over 15 min daily for 3 days starting 30 min before cyclophosphamide) at intervals of 4–6 weeks for a maximum of six courses. *Results*: Patients receiving FCA had equivalent rates of sepsis, early death, objective response and survival to those observed in a prior series of 78 patients treated with FC. Amifostine-associated toxicities included nausea, vomiting, and hypotension. *Conclusion*: The study amifostine regimen did not reduce the toxicity or activity of the FC regimen in patients with CLL.

Keywords Chronic lymphocytic leukemia · Amifostine · Fludarabine · Cyclophosphamide · Sepsis

Introduction

Fludarabine is the most active single cytotoxic agent in the treatment of patients with chronic lymphocytic leukemia (CLL) with response rates of approximately 80% and 60% in previously untreated and relapsed patients, respectively [1, 2, 3, 4]. As complete remission rates are low with single-agent fludarabine, and extramedullary toxicities limited, fludarabine-based combinations are being investigated in patients with CLL [5, 6, 7, 8, 9, 10, 11]. The most widely investigated combination is that of fludarabine and cyclophosphamide (FC) [6, 7, 8, 12, 13, 14, 15, 16, 17]. Cyclophosphamide was initially chosen for combination with fludarabine as it was an established effective single agent in patients with CLL [15, 18]. Data from in vitro studies indicate additive or synergistic activity of the FC combination [19]. The basis for potential synergy has been suggested to be that the increased capacity for excision repair in alkylating agent-resistant CLL cells facilitates incorporation of fludarabine and that fludarabine-induced inhibition of DNA repair enzymes enhances cyclophosphamide activity [19]. In a cohort of 128 patients with CLL, the FC regimen was associated with an 80–88% objective response (OR) rate in patients who were not refractory to single-agent fludarabine prior to study entry [8]. In patients who were refractory to prior fludarabine, the OR rate was 38%. The main toxicity of the FC regimen is infection with pneumonia or sepsis occurring in 25% of patients, and fever of unknown origin (FUO) in 30%.

Amifostine (WR-2721, Ethyol) is an organic thiophosphate being widely investigated as an agent that may selectively protect normal tissues from the toxicities of chemotherapy and radiation [20, 21]. Amifostine is a prodrug that is dephosphorylated at the tissue site to its active metabolite (WR-1065) by alkaline phosphatase. Differences in the alkaline phosphatase concentration in normal and tumor tissues result in greater conversion of amifostine to WR-1065 in normal tissues [20, 21]. Local differences between the pH of normal (neutral) and tumor (slightly acidic) tissue microenvironments lead to preferential uptake of WR-1065 by normal tissue [22]. Intracellularly, WR-1065 competes with the reactive moieties of alkylating agents for binding to DNA or RNA [23]. It also acts as a potent scavenger of the oxygen free radicals induced by chemotherapy and

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radiation therapy [24]. Amifostine has been shown in clinical studies to reduce the renal toxicity of cisplatin chemotherapy and to reduce myelosuppression associated with a number of cytotoxic agents, including cyclophosphamide, carboplatin, and mitomycin C [20, 25]. Amifostine has not been associated with a reduction in antitumor activity in any study to date. Patients with CLL are immunosuppressed by their leukemia, and additional myelosuppression leads to very high rates of sepsis-related mortality and morbidity [26, 27]. We thus conducted a phase II study to assess the efficacy of amifostine in reducing sepsis associated with the FC regimen in patients with CLL.

Materials and methods

Patients

Patients with CLL who required therapy were entered into the study after written informed consent was obtained according to institutional guidelines. All patients had pretreatment evaluation, including history and physical examination, complete blood counts, white blood cell (WBC) differential and platelet counts, biochemistry panel including liver and renal function studies, serum $beta_2$ microglobulin, serum immunoglobulins, bone marrow aspiration and biopsy, and marrow samples for immunophenotyping. Entry criteria were the same as those for the prior study of FC alone [8] and required (a) a confirmation of diagnosis with a monotypic expansion of lymphoid cells 10×10^9/l morphologically consistent with CLL (small lymphocytes), (b) more than 30% lymphocytes in the bone marrow, and (c) serum creatinine <2.0 mg% and serum bilirubin <2.0 mg%. Patients with Rai stages III and IV disease were eligible. Patients with Rai stages 0 to II were eligible if they had evidence of active disease as defined by the NCI-sponsored Working Group [28], i.e. increase in symptoms related to leukemia, including weight loss 10% over a 6-month period, temperature of 38°C without evidence of infection, worsening anemia or thrombocytopenia, progressive lymphocytosis with a rapid lymphocyte doubling time, marked hypogammaglobulinemia or paraproteinemia, extreme fatigue, massive or progressive hepatosplenomegaly, or massive or progressive lymphadenopathy.

Therapy

The FCA regimen was FC as previously published [8], i.e. fludarabine 30 mg/m^2 i.v. daily for 3 days and cyclophosphamide 300 mg/m^2 i.v. daily for 3 days given with amifostine 500 mg (fixed dose) i.v. over 15 min daily for 3 days commencing 30 min prior to cyclophosphamide (FCA). FCA courses were repeated every 28 to 42 days for a maximum of six courses with each course beginning when an absolute neutrophil count (ANC) of 1.5×10^9/l and platelet count of 75×10^9/l were documented. In patients with cytopenias due to marrow infiltration, recovery above pretreatment counts was considered adequate evidence of hematologic recovery to allow retreatment. FC doses were reduced by one dose level (fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2) in subsequent cycles if grade 3 or 4 extramedullary toxicities occurred. Fludarabine was reduced by one dose level for serum creatinine increase to 1.6 to 2 mg%, and by two dose levels (20 mg/m^2) for creatinine >2 mg%. Cyclophosphamide was reduced by two dose levels (200 mg/m^2) for grade 2–4 cystitis. The individual doses of either fludarabine or cyclophosphamide were reduced by one dose level for drug-specific grade 3 or 4 toxicity. Prophylactic growth factors were not used. Patients routinely received trimethoprim/sulfamethoxazole, fluconazole, and acyclovir prophylaxis orally. Patients received ondansetron and other nonsteroidal antiemetics as required prior to each amifostine infusion.

Sepsis data

The primary objective of the study was to assess the efficacy of amifostine in decreasing the incidence of sepsis associated with the FC regimen. The infection follow-up period was defined as the interval from initiation of treatment until 30 days following the first day of the last cycle of therapy, or time to therapy with another chemotherapy regimen because of disease progression or failure to respond, or death. For every patient and each cycle, the infection data were collected and each episode was classified as pneumonia, sepsis (a causative agent was identified), or FUO (temperature >38.3°C, no causative agent and site identified), herpes zoster virus (HZV) infection, herpes simplex virus (HSV) infection, or minor infection including upper respiratory tract (pharyngitis, sinusitis, or rhinitis), bronchitis, aerodigestive tract infection, urinary tract infection, skin and/or soft tissue infection, or low-grade fever requiring oral antibiotics and no hospitalization. If patients experienced more than one type of infection they were counted under each category [26]. Other toxicities were graded according the National Cancer Institute's (NCI) Common Toxicity Criteria version 2.0 (revised by NCI 3/23/1998, http://ctep.info.nih.gov).

Response criteria

Response criteria were those defined by the National Cancer Institute (NCI) Working Group [28]. Complete remission (CR) required the disappearance of all palpable disease, normalization of the blood counts (neutrophils $>1.5\times10^9$/l, platelets $>100\times10^9$/l, hemoglobin >11 g/dl), bone marrow aspirate lymphocyte percentage <30%, and no evidence of disease on bone marrow biopsy. A nodular partial remission (PR-nodular) required the same criteria as for CR with the exception that lymphoid nodules could be seen on bone marrow biopsy. A partial remission (PR) required 50% or more reduction in palpable disease as well as one or more of the remaining features: neutrophils 1.5×10^9/l or 50% improvement over baseline, platelets more than 100×10^9/l or 50% improvement over baseline, and hemoglobin more than 11.0 g/dl or 50% improvement over baseline without transfusions. After completion of therapy, patients were reevaluated at 3-month intervals with history, physical examination, blood counts and biochemical analysis. Bone marrow examination was performed every 6 months.

Statistical considerations

The incidence of septic events, response rates, and survival rates were compared, using the Kruskal-Wallis, Wilcoxon, and/or Chi^2 tests as appropriate, with those of a prior cohort of 78 patients treated on study with the same eligibility criteria, cytotoxic therapy (FC), and response and toxicity criteria [8].

Results

The clinical characteristics of 46 patients who received FCA on study are summarized in Table 1, as are the same characteristics of 78 patients in the retrospective control group. Other than a decrease in the number of patients treated with prior alkylating agents only (reflecting the increasing use of fludarabine as a front-line agent), there were no significant differences between the groups in terms of these characteristics. The 46 patients received a total of 170 cycles of FCA, and the 78 patients a total of 284 cycles of FC. The infection rates defined by category per patient and per total cycles of chemotherapy are detailed in Table 2. There were no

Table 1 Characteristics of patients treated with fludarabine and cyclophosphamide (FC) alone or FC with amifostine (FCA)

	FCA	FC
Number of patients	46	78
Age (years)		
> 60	59%	60%
≤ 60	41%	40%
Sex		
Male	67%	71%
Female	33%	29%
Rai stage		
I/II	56%	51%
III/IV	44%	49%
Number of prior regimens		
None	35%	29%
One	27%	31%
Two or three	28%	33%
Four or more	10%	7%
Prior treatment regimen		
None	30%	27%
Alkylating agent	7%	15%
Alkylating agent + fludarabine[a]	37%	36%
Alkylating agent + fludarabine[b]	26%	22%
$Beta_2$ microglobulin (mg/l)		
> 3.0	73%	64%
> 4.0	40%	41%

[a]Sensitive to last prior fludarabine treatment
[b]Refractory to last prior fludarabine treatment

significant differences in any category of infection. Of the 46 patients treated with FCA, 4 (9%) developed grade 3 or 4 nausea and vomiting, 4 (9%) grade 3 hypotension, and 2 (4%) grade 3 skin rashes associated with amifostine administration. The overall incidence of nausea and vomiting was low relative to that found in other studies, which may reflect the use of a lower amifostine dose and/or the aggressive use of antiemetic premedications in this study [29].

There was no evident impact of amifostine on the grade or duration of neutropenia or thrombocytopenia associated with FC therapy. The cumulative doses of cytotoxic agents did not differ between the groups. As the use of recombinant growth factors was allowed during an episode of infection at the discretion of the treating physician, we compared the use of these factors between study and control cohorts—no difference in the overall usage of growth factors was observed. There was no difference in the rate of hospitalization for therapy and/or complications of therapy between the two groups.

The rates of overall, CR and PR, and early death rate were equivalent in the FCA and FC patient cohorts, both overall and when stratified by type of prior therapy and fludarabine sensitivity or resistance at last prior exposure (Table 3). As illustrated in Fig. 1, survival was equivalent in both groups.

Discussion and conclusion

The FCA regimen failed to have any overt impact on the rates or types of sepsis occurring in patients with CLL receiving the FC regimen. This study was discontinued ahead of schedule because of withdrawal of support from the sponsoring company—we originally intended to treat a larger cohort of patients. The cohort of 78 patients were selected as a control group because they were treated immediately prior to the sequentially treated study cohort and had on file the complete data on adverse events, hospitalization rates, and supportive care necessary to make a valid comparison with the study cohort.

Neither maximal tolerated doses nor optimal schedules of amifostine have been identified [25, 30]. It is possible that the schedule we investigated was not optimal. Doses lower than that approved by the FDA are being investigated in many studies—recent data indicate that amifostine administered at this latter or even higher doses is variably effective in reducing myelosuppression with a variety of cytotoxic regimens, while decreasing the cytotoxic regimen tolerability [31, 32, 33, 34]. It is also possible that the cytoprotectant effects of amifostine may be specific to the cytotoxic agent or regimen. Although data on studies investigating the combination of amifostine and cyclophosphamide are encouraging [23, 35, 36, 37, 38, 39], no in vitro data on amifostine's interactions with purine analogs have been reported.

The focus on sepsis as an end-point in this study was because of the well-recognized vulnerability of patients with CLL to infectious agents [40]. Fludarabine therapy is associated with immunosuppression and myelosuppression that increases rates of sepsis, particularly with opportunistic infections, in patients with CLL [11, 41]. In a recent analysis of 518 patients randomized to receive fludarabine, chlorambucil, or fludarabine plus chlorambucil as first-line therapy for CLL, patients treated with fludarabine plus chlorambucil had significantly more infections than those receiving either single agent [11]. There were also more infections in patients who

Table 2 Incidence of infections in patients receiving FC (78 patients, 284 cycles) or FCA (46 patients, 170 cycles)

	Pneumonia	Sepsis	Fever of unknown origin	Herpes simplex virus	Herpes zoster virus	Minor infection	Any infection
Percent of patients							
FCA	20	12	35	11	4	26	59
FC	18	10	31	11	4	24	60
Percent of cycles							
FCA	6	4	12	3	1	9	32
FC	5	3	11	4	1	8	32

Table 3 Response to FCA and FC by prior treatment

Prior treatment	FCA				FC			
	No. of patients	Complete response (%)	Partial response (%)	Objective response (%)	No. of patients	Complete response (%)	Partial response (%)	Objective response (%)
None	14	36	50	86	21	33	52	86
Alkylating agent	3	0	66	66	12	17	58	75
Alkylating agent + fludarabine[a]	17	12	59	71	28	7	68	75
Alkylating agent + fludarabine[b]	12	0	42	42	17	6	35	41

[a]Sensitive to last prior fludarabine treatment
[b]Refractory to last prior fludarabine treatment

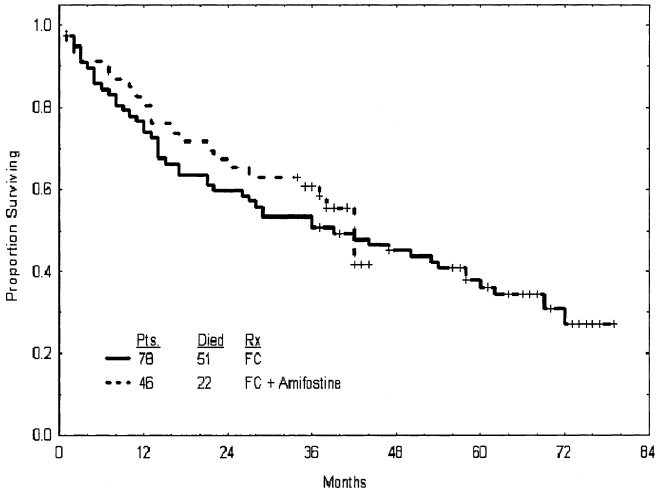

Fig. 1 Survival of patients treated with FC or FCA

received fludarabine only than in those who received chlorambucil only, particularly more major infections and herpes virus infections. Prophylaxis for *Pneumocystis carinii* and herpes viruses are usually incorporated into current fludarabine-based regimens in CLL and the coadministration of corticosteroids minimized [26, 42, 43, 44]. In the study population, no patient developed *P. carinii*, *Listeria*, *Nocardia*, or *Aspergillus* infection, which may in part reflect prophylactic therapy. Despite the use of antiviral prophylaxis, 15% of patients experienced at least one episode of HSV or HZV infection during FCA therapy.

Amifostine had no overt impact on the rates or degree of response to the FC regimen in patients with CLL. As in previous series of patients with CLL treated with fludarabine-based combinations [8, 42], the OR rate in patients receiving FCA was significantly lower in patients refractory to the last prior fludarabine regimen (42%) versus 71% in those sensitive to the last prior fludarabine regimen versus 86% in patients who had received no prior therapy. As in all previously reported studies in patients with solid tumors [20, 45, 46, 47], there was no evidence that the cytoprotectant effect of amifostine extended to tumor cells, as response rates and survival rates were equivalent between the FC- and FCA-treated patient cohorts.

Amifostine has had mixed results in terms of its ability to protect against adverse events related to cytotoxic administration [25, 46, 47]. It is currently FDA approved as an agent to reduce the cumulative renal toxicity associated with repeated cisplatin therapy in patients with ovarian or non-small-cell lung cancer [48]. The FDA indication states that amifostine should not be administered to patients in settings where chemotherapy can produce a significant survival advantage or cure, except in the context of a clinical trial. A recent update of the clinical practice guidelines of the American Society of Clinical Oncology on amifostine use does not recommend its use outside its indication or clinical studies [49].

Amifostine administration requires close patient monitoring and is associated with significant costs, both in terms of adverse events and resources [48]. In adults, the approved regimen of amifostine to be given with chemotherapy is 910 mg/m^2 administered i.v. over 15 min, 30 min before chemotherapy. All patients should be treated with antiemetics before the administration of amifostine, and pretreatment with i.v. fluids should also be considered. Blood pressure is taken every 3 to 5 min during the 15-min infusion. Amifostine is discontinued if the blood pressure declines significantly or the patient becomes symptomatic. Hypotension associated with amifostine usually occurs at the end of the infusion and is usually reversed by discontinuation of the amifostine, administration of saline, and placing the patient in the Trendelenburg position [49]. Amifostine toxicity is clearly dose-related [21, 47, 50, 51, 52]. In the FCA regimen, we incorporated a flat dose of 500 mg [53, 54, 55], which has been reported to be associated with a significant reduction in amifostine-related acute adverse events. Grade 3 or 4 adverse events associated with amifostine infusion in this study included nausea and vomiting (9% of patients), hypotension (9%), and skin rashes (4%); all responded promptly to therapy. There was a significant increase in the rates of these adverse events relative to the control group despite the "lower" dose of amifostine used which is associated with relatively fewer gastrointestinal adverse events [56].

Subcutaneous administration of amifostine is being investigated. This approach may make its incorporation into further studies more feasible [57].

Consistent with the currently reported data, Ghielmini et al. have recently reported that amifostine was ineffective in a dose-escalation study of patients with lymphoma receiving high-dose cyclophosphamide [30]. We have also observed no benefit from the administration of amifostine in a phase I study in which it was added to idarubicin and cytarabine therapy in patients with refractory acute myeloid leukemia or myelodysplastic syndromes [34]. Our current efforts to reduce the sepsis associated with the FC regimen are focused on the incorporation of recombinant growth factors into the regimen.

In a prior pilot study, the impact on sepsis of the addition of recombinant granulocyte colony-stimulating factor (G-CSF) to a single-agent fludarabine regimen was investigated [27]. In a cohort of 25 previously treated patients with CLL, the incidence of infection was compared with that seen in a historical control population of 145 patients given the same fludarabine regimen. While the incidence of pneumonia was significantly reduced, there was no apparent reduction in other infections [27]. As opportunistic infections are a particular problem in CLL patients, we are currently investigating the potential of recombinant granulocyte-monocyte colony-stimulating factor (GM-CSF) to reduce sepsis associated with the FC regimen where its ability to stimulate monocyte proliferation and function might be of particular benefit [58].

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