Modulation of AraC by Fludarabine: Results of Salvage Therapy by AMLCG

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Abstract. Fludarabine was shown to increase the intracellular formation of AraCTP during treatment with AraC both in vitro and in vivo and had significant activity in patients with advanced acute myeloid leukemia (AML) when used in combination with AraC in phase II studies. However, the efficacy of fludarabine as chemo-modulator of the AraC metabolism has not yet been assessed in phase III studies. Based on the S-HAI salvage regimen comprising high-dose AraC q 12 hours on days 1, 2, 8, and 9 and idarubicin on days 3, 4, 10, and 11, the German AML Cooperative Group initiated a prospective randomized comparison between fludarabine q 12 hours on days 1, 2, 8, and 9 in addition to S-HAI as compared with S-HAI alone. Of 91 patients having entered the ongoing study 66 are fully evaluable at the present time (median age 54 years, range 20-75). Twenty-five patients had refractory disease or early relapses, 39 patients had relapses after a preceding CR of more than six months duration and one patient had a second relapse. Thirty patients achieved a remission (CR, 45%; PR, 3%) while the non-response rate was 32% and 20% suffered from early death. The application of fludarabine resulted in a longer duration of neutropenia (38 versus 32 days). Severe non-hematologic toxicity (WHO III/IV) consisted mainly of nausea/vomiting (26% versus 13%), diarrhea (23% versus 10%), mucositis (14% versus 19%), and bleeding (11% versus 0%) and infectious complications included pneumonia (57% versus 39%), FUO (60% versus 45%), and bacteremia (49% versus 16%). The sequential test has not yet decided for either superiority of fludarabine or equality of both study arms.

Introduction

Cytosine arabinoside (AraC) is the most active single agent in the treatment of adults with acute myeloid leukemia (AML) and provides the basis for most currently used regimens [26]. A substantial improvement of the antileukemic efficacy of the drug has been achieved both in patients receiving first line combination regimens and in cases undergoing salvage therapy by applying higher than conventional doses of AraC [10,32,38]. In attempts to further increase the activity of AraC-containing regimens, fludarabine has been added as a chemo-modulator to augment the intracellular levels of AraC triphosphate (AraCTP) which is the main cytotoxic metabolite of AraC. Pharmacokinetic investigations revealed that, following intracellular phosphorylation of fludarabine, the resulting triphosphate acts as an inhibitor of ribonucleotide reductase, which catalyzes the de novo synthesis of deoxynucleotides. As a consequence, the intracellular levels of these compounds are depleted leading to a diminished inhibition of deoxycytidine kinase. Since this enzyme catalyses the initial and rate-limiting step in the synthesis of AraCTP, i.e. the phosphorylation of AraC to its mono-

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phosphate, an overall increase in intracellular levels of AraCTP results, which has been demonstrated in AML blasts both ex vivo and in vivo [22,23]. In several phase II studies applying the fludarabine/AraC regimen [20,46] or combinations of both drugs with G-CSF [21,29,40,41,49] and anthracyclins [17,42] a significant antileukemic efficacy was demonstrated in patients with high-risk AML. CR rates of up to 74% have been achieved with these combinations, although most studies included a small number of patients only. However, the use of fludarabine as a chemomodulator of the AraC metabolism has not yet been proven in a randomized phase III trial. Therefore, the current study addressed the question of improving the activity of a high-dose AraC based regimen by fludarabine on the basis of a prospective randomized comparison of applying fludarabine in addition to the sequential high-dose AraC and idarubicine (S-HAI) regimen versus S-HAI alone in patients with refractory and relapsed AML.

Patients and Methods

Patients

Consecutive patients at ages 18 or older with relapsed and refractory AML who were admitted at the participating centers between April 1996 and February 1999 were eligible for the study. The diagnosis of AML was based on the revised French-American-British (FAB) Group criteria [7]. Refractoriness against standard chemotherapy was defined according to previously established criteria [28]: These included

- primary resistance against two cycles of induction therapy;
- first early relapse with a remission duration of less than 6 months;
- second and subsequent relapse.

Patients with first relapses after six months remission duration were not considered refractory to standard therapy and were included as relapsed AML.

All patients were recruited from the first line trials of the German AML Cooperative Group and had thus received a standardized first line treatment. In patients less than 60 years of age first line therapy consisted in double induction therapy with the sequential application of the nine-day-regimen of thioguanine, AraC, daunorubicin (TAD-9) followed by high-dose AraC and mitoxantrone (HAM). Older patients all received one course of TAD-9 and were treated by a HAM course only upon inadequate response to TAD-9. Patients of all ages who achieved a complete remission (CR) subsequently received TAD-9 for consolidation and monthly maintenance therapy for three years [14,15].

Patients with a preceding allogeneic bone marrow transplantation were excluded from the study. Further exclusion criteria comprised coronary heart disease; heart failure; cardiomyopathy; severe arterial hypertension; abnormal liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase [AP] more than three times the upper normal limits; total bilirubin > 2.0 mg/dl); impaired renal function (serum creatinine > 2.0 mg/dl); severe infections; or pregnancy.

Antileukemic Therapy

Patients meeting the entry criteria were enrolled into the current study and were treated by S-HAI [34] comprising AraC every 12 hours by a 3-hour infusion on days 1, 2, 8, and 9 and idarubicine 10 mg/m²/day as a 30-min infusion on days 3, 4, 10, and 11, respectively (Fig. 1). Based on the results of a previous study comparing two dose levels of high-dose AraC [32], patients younger than 60 years with refractory disease, early relapse following a first CR of less than six months, or second and subsequent relapses received AraC at doses of 3.0 g/m² per application while all other patients were treated with 1.0 g/m² AraC per single dose. All patients were randomly assigned to receive fludarabine in addition to S-HAI or S-HAI alone. Patients randomized for fludarabine received the drug at 15 mg/m² as a 30-min infusion four hours prior to each AraC administration, i.e. twice daily on days 1, 2, 8, and 9. To avoid imbalances in the patients’ risk profile randomization was stratified for the following criteria: