Azacytidine for acute myeloid leukemia in elderly or frail patients: a phase II trial (SAKK 30/07)

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Abstract
This phase II trial treated elderly or frail patients with acute myeloid leukemia (AML) with single-agent subcutaneous azacytidine at 100 mg/m(2), on 5 of 28 days for up to six cycles. Treatment was stopped for lack of response, or continued to progression in responders. The primary endpoint was response within 6 months. A response rate ≥ 34% was considered a positive trial outcome. From September 2008 to April 2010, 45 patients from 10 centers (median age 74 [55-86] years) were accrued. Patients received four (1-21) cycles. Best response was complete response/complete response with incomplete recovery of neutrophils and/or platelets (CR/CRi) in eight (18%; 95% confidence interval [CI]: 8-32%), 0 (0%) partial response (PR), seven (16%) hematologic improvement, 17 (38%) stable disease. Three non-responding patients stopped treatment after six cycles, 31 patients stopped early and 11 patients continued treatment for 8-21 cycles. Adverse events (grade ≥ III) were infections (n = 13), febrile neutropenia (n = 8), thrombocytopenia (n = 7), dyspnea (p = 6), bleeding (n = 5) and anemia (n = 4). Median overall survival was 6 [...]
Azacytidine for acute myeloid leukemia in elderly or frail patients: a phase II trial (SAKK 30/07)

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Introduction

Acute myeloid leukemia (AML) in the elderly is difficult to treat. Combination chemotherapy and stem cell transplant have improved outcomes for younger patients [1,2]. AML is, however, a disease of older adults, with an annual incidence of approximately 15 in 100,000 in those 60 years of age or older, representing more than two-thirds of all reported cases [3]. Older patients do not tolerate intensive chemotherapy, and even if chemotherapy is given, rates of complete remission are low and very few survive long-term [4]. Poor outcome in older patients with AML is due to unfavorable characteristics of the leukemia, as well as comorbidities, poor performance status or organ dysfunction, limiting treatment options. AML in older patients may be the result of transformation from myelodysplastic syndrome, conferring a poor prognosis, and is more likely to present with poor-risk cytogenetics [5].

No standard of care is established in these patients. Low dose subcutaneous cytosine arabinoside has been shown in a trial by the medical research council (MRC) to prolong survival compared to hydroxyurea. In this trial the complete response (CR) rate on low dose cytosine arabinoside was 18%, and survival increased. It was mainly patients with low and intermediate risk disease who benefited from this treatment [6]. Numerous new substances have been tested for activity in AML, but in young patients anthracyclines and cytosine arabinoside remain the standard of care. In older patients all new treatment approaches have to be measured against either best supportive care, or low dose subcutaneous cytosine arabinoside [7-9].

The cytidine nucleoside analog azacytidine, a hypomethylating agent, has recently been shown to improve survival in patients with myelodysplastic syndrome (MDS) [10,11]. Azacytidine was also associated with significant improvements in other clinically relevant outcomes, including reductions in transfusion need, hospitalization and intravenous antimicrobial use [12]. This improved outcome...
has also been seen in patients with MDS hitherto classified as MDS RAEBt (refractory anemia with excess blasts in transformation), and according to the 2008 World Health Organization (WHO) classification of tumors of hematological or lymphoid tissues as AML with a blast count of 20–30% [13]. The mechanism of action of azacytidine is thought to be through incorporation into both DNA and RNA. DNA incorporation decreases DNA hypermethylation, allowing the re-expression of previously silenced genes that may include tumor suppressor genes [14]. We present here the results of a phase II trial treating elderly or frail patients with AML not eligible for intensive chemotherapy with subcutaneous azacytidine.

Patients and methods

This open-label single-arm phase II trial evaluated the efficacy of 5-azacytidine in newly diagnosed patients with AML not suitable for induction type chemotherapy due to age, comorbidities or unwillingness to undergo chemotherapy, with a WHO performance status ≤ 3. Patients had to have ≥ 20% blasts in the blood or bone marrow, or extramedullary disease; AML diagnosis classified by WHO criteria; de novo AML or AML secondary to prior hematological disease or secondary to cytotoxic treatment. Trial therapy consisted of azacytidine 100 mg/m² injected subcutaneously on 5 consecutive days every 28 days for up to six cycles, stopping at six cycles if no response higher than cutaneously on 5 consecutive days every 28 days for up to six cycles, stopping early in the case of progression or complications, and continuing beyond 6 months for responding patients.

The trial (Clinical Trial number: NCT00739388) was conducted in accordance with the Declaration of Helsinki, and was approved by Swissmedic and the ethics committees of the participating centers. Written informed consent was obtained from all patients.

Endpoint and statistical consideration

The primary endpoint of this phase II trial was defined as best response (defined as complete response/complete response with incomplete recovery of neutrophils and/or platelets [CR/CRI] or partial response [PR]) within 6 months of starting treatment. CR was defined as morphologic leukemia-free state and absolute neutrophil count (ANC) ≥ 1.0 × 10⁹/L, platelet count ≥ 100 × 10⁹/L (≥ 3 days after the last transfusion); CRI was defined as CR with incomplete recovery of the ANC and/or platelet count (≥ 3 days after the last transfusion); PR was defined as ANC ≥ 1.0 × 10⁹/L, platelet count ≥ 100 × 10⁹/L (≥ 3 days after the last transfusion) and blasts in the bone marrow should have decreased by ≥ 50% (relative to baseline) and reached a value of ≤ 25%. Secondary endpoints were time to response, response duration, time to and duration of HI as defined in the revised response criteria [15], event-free survival defined as the time from trial registration until progression, relapse or death from any cause, whichever occurred first, overall survival, adverse events and time spent in the hospital. Time-to-event endpoints were analyzed by the Kaplan–Meier method. Median follow-up time was calculated using the inverse Kaplan–Meier method.

The exact single-stage phase II design by A’Hern was used to calculate the required sample size for the primary endpoint. A response rate of ≤ 15% was considered uninteresting to pursue this treatment approach further, and a response rate of ≥ 34% was considered promising. With a significance level of 0.05 and a power of 90%, 43 patients were to be included. At the final analysis, if ≤ 10/43 (23%) patients showed a response, the trial treatment should be considered as uninteresting, otherwise promising.

Results

From September 2008 to April 2010, 47 patients were accrued across 10 centers in Switzerland. Two patients were not evaluable: they did not receive trial medication and had early disease-related death, leaving 45 patients with a median follow-up of 26 months for analysis. Median age of the 45 evaluable patients was 74 (range: 55–86) years, 27 (60%) were male and 34 (76%) patients had performance status 0–1. Details of the patient population are shown in Table I. Patients received a median number of 4 (range: 1–21) cycles. Three patients stopped treatment after six cycles because of lack of response. Eleven patients continued treatment to 8–21 cycles and stopped for progressive disease or relapse (10 patients) or refusal (one patient). Thirty-one patients had stopped treatment without completing the six cycles because of toxicity in four (9%), patient refusal in two (5%),
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Persistent or progressive disease in 15 (33%) and death with leukemia in 10 (22%). Of these 10 dead patients the immediate cause of death was leukemia in four, infection in four, cardiac failure in one and bleeding in one.

Among all 45 patients, eight (18%; 95% confidence interval [CI]: 8–32%) achieved a CR/CRi, no patients achieved a PR, seven (16%) had HI and 17 (38%) patients had stable disease as best response within 6 months. Details are shown in Table II. In these eight responding patients, treatment was terminated after 4–21 cycles for relapse/progression (five patients), death (one patient), refusal (one patient) and other reason (one patient). Median response duration in patients achieving CR/CRi was 8 (range: 4–21) months.

Table II. Results.

<table>
<thead>
<tr>
<th>Best response within 6 months</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRi</td>
<td>8</td>
<td>17.78</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Hematologic improvement</td>
<td>7</td>
<td>15.56</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17</td>
<td>37.78</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7</td>
<td>15.56</td>
</tr>
<tr>
<td>NA (2 withdrawal, 3 death*)</td>
<td>6</td>
<td>13.33</td>
</tr>
</tbody>
</table>

Table II Results.

<table>
<thead>
<tr>
<th>Time to CR (months, median, range)</th>
<th>4 (2–6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response duration (months, median, range)</td>
<td>8 (4–21)</td>
</tr>
<tr>
<td>Treatment cycles received (median, range)</td>
<td>4 (1–21)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
</tr>
<tr>
<td>No. of patients hospitalized</td>
<td>35</td>
</tr>
<tr>
<td>Duration (days, median, range)</td>
<td>23 (1–80)</td>
</tr>
<tr>
<td>No. of patients hospitalized first cycle of treatment</td>
<td>27</td>
</tr>
<tr>
<td>Duration during first cycle</td>
<td>13 (1–30)</td>
</tr>
<tr>
<td>(days, median, range)</td>
<td></td>
</tr>
</tbody>
</table>

CR/CRi, complete response/complete response with incomplete recovery of neutrophils and/or platelets; PR, partial response; NA, not available.

*Cause of death: subdural hematoma (1), pneumonia (1) and cardiac failure (1).

Toxicities of the treatment appeared to be manageable, and most reported adverse events were attributable to marrow failure in association with the disease or with infections. Seventy-three serious adverse events (SAEs) were reported...
in 36 patients. Most frequently reported adverse events of grade III or higher were infections in 13, febrile neutropenia in eight, thrombocytopenia in seven, dyspnea in six, neutropenia in six, bleeding in five and anemia in four patients, and are shown in Table III.

**Discussion**

Best treatment options for older patients with AML remain poor. There is controversy about how to treat these patients, given the heterogeneous disease presentation and unfavorable outcome. Older patients with AML have a poor prognosis, with a median survival time of less than 1 year. Treatment by supportive care alone is still a serious consideration. With the exception of low dose subcutaneous cytosine arabinoside, no drug has been shown to be effective in comparison to supportive care alone [6]. AML in the elderly is a heterogeneous disease, and age, comorbidities and tumor biology exemplified by cytogenetic risk groups are prognostic factors [5]. New therapeutic approaches are needed, particularly with improved toxicity, for administration in elderly patients.

This open-label phase II trial studied the subcutaneous administration of azacytidine to treat unselected elderly patients with AML not eligible for intensive chemotherapy. Based on data in patients with MDS and on data from patients with MDS RAEBt, which has been reclassified by WHO as AML with low blast counts, we considered a response rate of 35% or more to be promising enough to continue further with this approach, and a response rate of 15% or less to be uninteresting. While the response rate considered to be of clinical importance was not reached, there were eight patients (18%) who achieved a CR/CRi and an additional seven patients with HI, thus totaling some clinical benefit at 17/45 patients (38%), although this was short-lived in many. We could not identify factors clearly associated with response, with the possible exception of blast count at diagnosis. Patients with lower blast counts were more likely to achieve a response, although a statistical significance was not reached. Finally, the small number of patients did not allow us to draw conclusions on which cytogenetic and/or molecular defined subgroup of patients with AML might preferentially benefit from azacytidine treatment.

Side effects of this treatment were moderate. Reported severe adverse events were more likely to be associated with the disease than caused by the treatment. This trial administered azacytidine in a schedule and dose slightly different from what has been approved in patients with myelodysplastic syndrome, i.e. 100 mg/m² for 5 days instead of 75 mg/m² for 7 days, the cumulative monthly dose being almost identical. This schedule was chosen to facilitate outpatient administration on weekdays without requiring drug to be given over the weekend. Among the unexpected side effects, one patient had worsening renal function and one patient had retinal detachment. It is, however, difficult to determine in these patients whether there was any relationship with the trial drug or whether these effects could be attributed to infection and/or leukemia.

Other investigators have studied hypomethylating agents such as azacytidine and decitabine in patients with AML.
of importance are comparisons with studies using hypomethylating agents as single-agent treatment for AML. These studies confirmed responses in a minority of patients as comparable to those shown in the present study, and differences may be explained by differences in patient risk profiles.

The present results show that the modified azacitidine schedule as tested here is a feasible option for elderly or frail patients with AML in an outpatient setting with moderate, mainly hematologic, toxicity and response in a small proportion of patients, although the predetermined level of expected efficacy was not reached. The overall survival of the patient cohort does not appear to be very different from experience in similar patients, and it does not appear that single-agent azacitidine has a major impact on the outcome of AML in the elderly. Whether the dosing choice for this study had an impact on the rather low response rate cannot be determined. Further studies will need to address different treatment schedules and the use of azacitidine in combination with other drugs and a comparison with standard treatment approaches such as low-dose subcutaneous cytosine arabinoside.

Acknowledgements

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References