Stable remission after administration of the receptor tyrosine kinase inhibitor SU5416 in a patient with refractory acute myeloid leukemia

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The small molecule receptor tyrosine kinase (RTK) inhibitor SU5416 targets the vascular endothelial growth factor receptor 2 and the stem cell factor receptor c-kit. Herein is described the successful treatment of a 65-year-old woman with SU5416, in second relapse of acute myeloid leukemia (AML) and refractory toward standard chemotherapy regimens. After 12 weeks of treatment with SU5416, the blast cell counts (blood and bone marrow) decreased to undetectable levels and the peripheral blood cell counts normalized with the exception of the platelet count (50-80 × 10^9/L [50-80 × 10^9] μL). The duration of the remission is longer than 4 months during maintenance therapy with SU5416. Microvessel density in the patient’s bone marrow dropped from 33.4 to 12.3 microvessels/500-field 8 weeks after SU5416 administration and remains in the normal range. This is the first report of a stable remission achieved after administration of the RTK inhibitor SU5416 in a patient with AML relapse. (BLOOD. 2001;98:241-243)

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prevent hypersensitivity reactions related to the drug or to excipients in the formulation, such as polyoxyethylated castor oil (Cremophor), polyethyleneglycol or absolute ethanol, the patient received prophylaxis with histamine antagonists (2 mg clemastin iv and 400 mg cimetidine iv) plus 10 mg dexamethasone iv prior to each infusion of SU5416. The dose of dexamethasone was reduced to 4 mg at the fourth and to 2 mg at the subsequent infusions. The safety of SU5416 was assessed through physical examinations, vital signs, toxicity assessments, electrocardiography, and laboratory tests (hematology, coagulation, and clinical chemistry). In July 2000, treatment with SU5416 was started. Subsequently, a continuous decrease of the blast infiltration in the bone marrow and an increase of the peripheral blood cell counts were observed. The patient completely recovered from pneumonia and the pleural/pericardial effusions resolved.

Six weeks after initiation of SU5416 treatment, the patient developed symptomatic leukemic meningitis with right facial nerve palsy and 1245/3 leukemic blast cells in the cerebrospinal fluid (CSF). This was the first time that the patient had evidence of central nervous system involvement. SU5416 was continued and additional treatment with intrathecal chemotherapy (40 mg Ara-C, 15 mg methotrexate, 4 mg dexamethasone; twice a week) was started for 2 weeks followed by cranial irradiation (whole-brain dose of 30 Gy administered in 3 weeks). Subsequently, the patient received a second course of intrathecal chemotherapy applying the same dose and schedule for 3 weeks, thus achieving a complete resolution of the neurologic deficit and absence of leukemic blasts in repeated CSF specimens. Three months after the initiation of treatment with SU5416, the leukemic blast infiltration dropped to undetectable levels as determined by bone marrow morphology and immunophenotyping by flow cytometry with almost complete normalization of the peripheral blood cell counts.

Methods

Cytogenetic analyses, flow cytometry studies, and cytogenetic analyses were performed on bone marrow aspirates using standard methodology. The determination of the degree of angiogenesis was performed by immunohistochemical identification of microvascular endothelial cells with anti-human thrombomodulin antibodies as described.\(^2\) The median and interquartile range for the microvessel densities of 22 control patients was 13.2 and 11.4 to 14.8/×500-field, respectively. This corresponds to the average number of microvessels counted in a 0.126 mm\(^2\) field area at ×500 magnification using light microscopy.\(^3\) Immunostaining for VEGFR-2 was done in paraffin-embedded bone marrow specimens with a specific monoclonal antibody (anti–Flk-1, Santa Cruz Biotechnology, Santa Cruz, CA, sc-6251) using the alkaline phosphatase/anti–alkaline phosphatase double-bridge technique (Dako-APAAP Kit; Dako, Glostrup, Denmark).

Results and discussion

After proving to be refractory toward chemotherapy with mitoxantrone/etoposide and subsequent thalidomide, the patient received SU5416 for the second AML relapse. During SU5416 monotherapy, a steady decrease in the bone marrow blast cell infiltration was observed, accompanied by an increase in hemoglobin levels (data not shown) and the platelet and neutrophil counts (Figure 1A-B). This remission (<5% blasts in the bone marrow by morphology and immunopheno-tying with flow cytometry, neutrophils >1.5 × 10\(^9\)/L [1500/µL] and hemoglobin >110 g/L [11 g/dL], untransfused) has been sustained for more than 4 months since the SU5416 maintenance therapy using the same dosing schedule. The platelet counts increased to 60-80 × 10\(^9\)/L [60-80 × 10\(^9\)/µL] (Figure 1B). Thus, the patient fulfilled all but one (platelets ≥100 × 10\(^9\)/L [100 × 10\(^9\)/µL]) criteria for a CR according to a consensus definition\(^3\) or the criteria of CR\(_P\) (CR criteria without platelets ≥100 × 10\(^9\)/L [100 × 10\(^9\)/µL]) as used by others.

During the SU5416 treatment period of more than 7 months, no adverse events were observed. This is in line with the rather favorable side effect profile observed in previous phase I/II clinical trials in patients with advanced malignancies (Sugen, data on file). The only side effect was temporary somnolence lasting 2 to 3 hours after each infusion and not interfering with daily activities. This somnolence was most likely attributable to the premedication with the histamine antagonist clemastin.

At the time of second relapse, microvessel density in the bone marrow of the patient was 2.5-fold higher than the median of the control group, comparable with the values obtained at first diagnosis of the patient’s AML (Figure 1A). The increased microvessel density dropped from 33.4 to 12.3 microvessels/×500-field 8 weeks after the beginning of SU5416 administration and remained in the normal range during maintenance therapy with SU5416 (Figures 1A, 2A,C). The latter values are comparable to those obtained in CR after induction chemotherapy (Figure 1A). A parallel decrease of c-kit (detected by flow cytometry, data not shown) and VEGFR-2-positive leukemic blasts was observed (Figure 2B,D).

The case we present here is the first to demonstrate that the RTK inhibitor SU5416 induces a stable remission in a patient with AML relapse, refractory toward multiple standard chemotherapy regimens. SU5416 targets the VEGFR-2 as well as the SCF receptor c-kit. It has been demonstrated that SU5416 induces apoptosis in endothelial cells of a colon cancer animal model expressing VEGFR-2\(^3\) and in a c-kit–positive human myeloid leukemia cell line.\(^4\) In addition to the expression of c-kit, the patient discussed here had high levels of VEGF (data not shown) and VEGFR-2
expression of the leukemic blasts as demonstrated by immunohistochemistry in the bone marrow specimens (Figure 2B). This is in line with a recent report of strong VEGFR-2 expression in human chloromas.7 Thus, VEGF produced by the patient’s leukemic blasts may have supported leukemic cell growth through paracrine (by increasing the bone marrow endothelial cell mass) and autocrine (supporting leukemic cell survival) mechanisms. Therefore, the observed remission in this patient might be due to the combination of antiangiogenic (targeting VEGFR-2 on endothelial cells) and antileukemic effects (targeting both VEGFR-2 and c-kit on leukemic blast cells) thus blocking paracrine and autocrine loops induced by leukemia-derived VEGF. This hypothesis is supported by the observed decrease in bone marrow microvessel density, VEGFR-2 expression, and blast cell infiltration.

Despite the observed antiangiogenic and antileukemic effects in the bone marrow, SU5416 did not prevent the occurrence of symptomatic leukemic meningitis in the sixth week of treatment. This might suggest that SU5416 has not sufficiently crossed the blood-brain barrier. On the other hand, we cannot completely exclude that the intrathecal administration of chemotherapy, especially Ara-C, contributed to the observed remission due to systemic resorption. However, a major contribution of Ara-C is rather unlikely when considering that the decrease of the bone marrow blast infiltration from 90% to 20% and the recovery of the peripheral blood cell counts had already occurred before starting intrathecal chemotherapy (Figures 1A-B). Furthermore, the cumulative dose of Ara-C before the observed remission was low (160 mg) and the ongoing remission during SU5416 maintenance therapy for more than 3 months after the last intrathecal chemotherapy underscores the antileukemic efficacy of SU5416.

In conclusion, targeting VEGFR-2 might be a promising therapeutic option in the treatment of AML and should be further evaluated in controlled clinical trials.

Note added in proof. A third AML relapse occurred 9 months after institution of SU5416 treatment.

References

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