Radical surgery and venetoclax plus azacitidine in an octogenarian with acute myeloid leukemia

A 79-year-old female patient was admitted in December 2020 to our hospital due to swelling and redness of her left forearm (Figure 1A). Besides arterial hypertension and a history of sleep apnoea her medical history was unremarkable. Laboratory evaluation revealed a decreased white blood cell count (WBC) of 0.8x10^9/L (range, 3.5-9.8x10^9/L), a hemoglobin value of 11.6 g/dL (range, 13.5–17.5 g/dL) and platelet count of 112x10^9/L (range, 140–360x10^9/L). A differential blood cell count showed 16% myeloid blast cells. Moreover, laboratory evaluation revealed acute renal failure with a creatinine of 128 μmol/L (range, 45-84 μmol/L) and massively elevated C-reactive protein (CRP) of 229 md/L (range, <5 mg/L). Renal insufficiency improved rapidly and creatinine values normalized within 5 days due to the application of intravenous fluids. Bone marrow evaluation showed myeloid blast cells of 58%. Cytogenetic analysis revealed a complex karyotype (90,XXXX,-17,-21[12]/47,XX,+8[8]/46,XX[7]) and molecular analysis an *IDH2* R172K mutation. All other tested mutations (*CEBPA, IDH1, NPM1, FLT3*-ITD*, FLT3*-TKD) were unmutated. Thus, the diagnosis of acute myeloid leukemia (AML) with myelodysplasia-related abnormalities was made[1] and the patient was classified as high-risk.[2]

The swelling and reddening on the left forearm were diagnosed as phlegmone and treatment with broad-spectrum antibiotics (clindamycin 600 mg orally, three times daily; meropenem 1 g intravenously, three times daily) as well as mold-active antifungal prophylaxis with posaconazole was started immediately. A computed tomography (CT) scan showed extensive phlegmonous-inflammatory changes of the skin and tissue. Thus, surgical intervention with rapid debridement was urgently indicated. The infection was split surgically, showing a partially avital muscle extensor carpi ulnaris without signs of necrotizing fasciitis. Besides necrosectomy, partial resection of the muscle and fascia were performed, which was covered with synthetic wound dressing (Figure 1B). Histopathological analysis revealed an avital tissue of the muscle and tendon without signs of malignancy, bacteria or necrotizing fasciitis. After surgical intervention, all fingers were moveable and sensitivity was intact. Overall, two surgical wound revisions had to be performed within 5 days with additional necrosectomy, resulting in a severe lesion, which had to be covered with an autologous mesh graft from her left thigh. We started AML treatment with azacitidine (AZA) 75 mg/m² subcutaneously, days 1-5 and venetoclax (VEN) 100 mg orally (dose ramp-up), days 1-18 on day 7 after diagnosis of AML and improvement of the wound conditions. VEN/AZA were dose-reduced due to severe infection as well as concurrent antifungal prophylaxis with posaconazole. No signs of tumor lysis syndrome occurred. Besides, therapy with broad-spectrum antibiotics was continued. In the following 2 weeks, three additional surgical interventions were required for the installation and changing of a vacuum pump. Surprisingly, the wound conditions improved drastically despite AML treatment (Figure 2A). Thus, antibiotics were reduced to monotherapy with meropenem 1 g intravenously three times daily on day 13 after admittance. Overall, only two packed red blood cells were transfused during the first cycle of VEN/AZA.

First AML response assessment was performed on day 13 after the start of VEN/AZA treatment. Bone marrow cytology revealed a decline of myeloid blast cells to 11%. Thus, VEN was stopped on day 18 to allow further wound healing and ingrowing of the mesh graft. Repeated bone marrow evaluation on day 20 showed a further decline to 9% myeloid blast cells. The patient was still bicytopenic with WBC of 0.9x10^9/L (range, 3.5-9.8x10^9/L), a hemoglobin value of 7.3 g/dL (range, 13.5–17.5 g/dL), whereas the platelet count rose spontaneously to 194x10^9/L (range, 140–360x10^9/L). The vacuum pump was removed 23 days after installation.

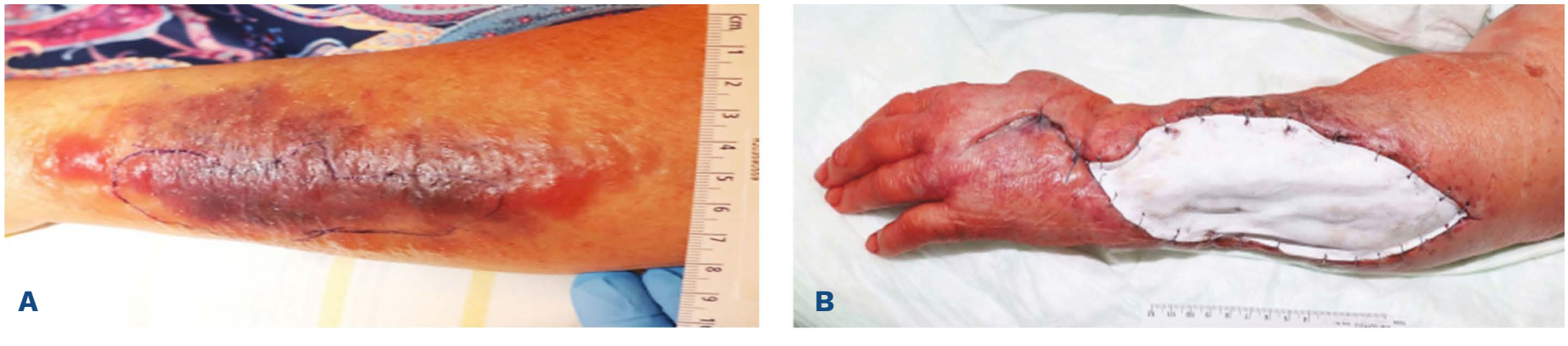

Figure 1. Picture of left arm of the patient with acute myeloid leukemia. (A) Left arm at diagnosis showing an infection with edematous swelling and redness. (B) Left arm after first surgery showing the synthetic wound dressing.

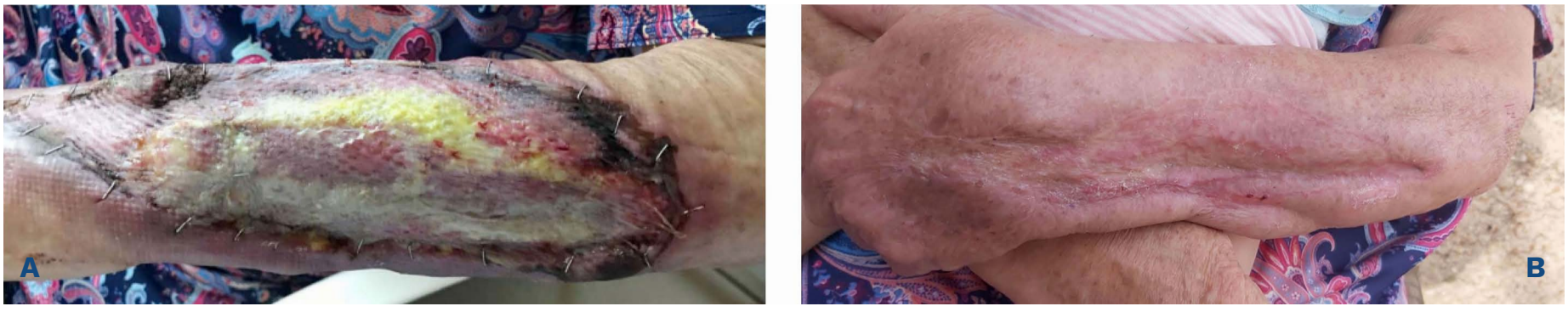

Figure 2. Picture of the left arm of the patient with acute myeloid leukemia. (A) Autologous mesh graft and (B) complete wound healing roughly 5 months after diagnosis of acute myeloid leukemia.

Hematologic recovery with WBC 2.2x10^9/L, a hemoglobin value of 8.9 g/dL and platelet count of 238x10^9/L occurred 12 days after VEN was stopped.

Thus, the patient could be discharged 43 days after admission to our hospital. Antibiotics were reduced to oral prophylaxis with ciprofloxacin 500 mg twice daily.

After discharge, the patient was followed-up routinely in our outpatient department for continuation of VEN/AZA treatment in reduced dosage (AZA 75 mg/m² subcutaneously, days 1-5; VEN 100 mg orally once daily, days 1-14, repeated every 28 days) due to concurrent antifungal prophylaxis with posaconazole. After the second cycle of VEN/AZA treatment bone marrow evaluation revealed complete remission (CR). Besides, the *IDH2* mutation was no longer detectable by digital droplet polymerase chain reaction (sensitivity of 1:10,000 for mutated to wild-type *IDH2*).[3] The therapy was continued for two more cycles. Thereafter, VEN/AZA treatment was suspended for 6 weeks due to patient's wish. In the following cycles the dosage of VEN/AZA was continued as before to prevent hematologic toxicity (AZA 75 mg/m² subcutaneously, days 1-5; VEN 100 mg orally once daily, days 1-14; repeated every 28 days). Treatment with VEN/AZA was well tolerated and no grade 3 or higher toxicity occurred.

The wound improved further and finally healed after roughly 5 months (Figure 2B). A recent follow-up phone call in September 2022 revealed that the patient is feeling well roughly 20 months after start of treatment. VEN/AZA treatment is continued as stated above in a close-to-home outpatient setting and AML is still in CR.

The combined therapy of VEN and hypomethylating agents (HMA) has led to high CR and improved overall survival rates in newly diagnosed AML not eligible for intensive chemotherapy as compared to monotherapy with HMA,[4] leading to the recent Food and Drug Administration and European Medicine Agency approval of VEN in combination with HMA or low-dose cytarabine for older adults with newly diagnosed AML.[5] Particularly, impressive survival benefit was shown in patients with *IDH2*- or *NPM1*-mutated AML.[6] Indeed, continued treatment with VEN/AZA resulted in a deep and durable molecular remission in our patient, who harbored an *IDH2* mutation at diagnosis. Thus, VEN/AZA seems currently the best option for older patients with newly diagnosed AML and one of the aforementioned mutations.

One of the main obstacles in AML therapy and one of the main reasons for early death are infections due to immunosuppression of the underlying disease as well as myelotoxic effects of the therapy.[7] We here present the first case of successful VEN/AZA treatment despite a severe infection, requiring repetitive surgical interventions.

VEN-based regimens are associated with significant myelosuppression, requiring dose adjustment.[8] The currently recommended dose of VEN in case of concurrent treatment with strong CYP3A4 inhibitors (posaconazole) is 50 mg/daily.[8] In our case, we decided to reduce both, the duration of VEN/AZA as well as the dose of VEN due to significant comorbidities and concurrent antifungal prophylaxis with posaconazole. Antifungal and antibiotic prophylaxis was given only in case of neutrophil count below 0.5x10^9/L. The patient tolerated the therapy very well without any further toxicities or need to use granulocyte colony stimulating factor. Currently, we continue with lower-intensity VEN/AZA treatment indefinitely.

To date, the optimal treatment duration of VEN-based lower-intensity regimens is unknown.[8] However, patients aren't particularly enamored with the concept of treatment with parenteral VEN/AZA extending indefinitely. Thus, finding some way of using oral VEN/AZA would seem to be an urgent clinical approach.[9] Some patients with VEN-sensitive genomics, such as *NPM1* and *IDH2* mutations, who are in deep remission might also be candidates for treatment discontinuation and active surveillance.[10]

In conclusion, VEN/AZA seems to be safe and feasible, even in patients with severe infections, although larger data are needed for further evaluation.

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Contributions

FR and SK were responsible for the concept of this paper, contributed to the literature search data collection, treated the patient, analyzed and interpreted data, and wrote the manuscript; RH treated the patient and critically revised the manuscript; AM performed research and critically revised the manuscript. All authors approved the submission.

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Questions regarding data sharing should be addressed to the corresponding author.

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