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## Repeated responses of an elderly patient with high-risk myelodysplastic syndrome to sequential therapy with tipifarnib, 5-azacitidine, and decitabine

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Dear Editor,

Patients with myelodysplastic syndromes (MDS) and a medullary blast count of more than 10% have a median survival of about 1 year. Intensive treatment approaches like induction chemotherapy and allogeneic stem cell transplantation offer a curative approach, but are not feasible for the vast majority of patients due to age and/or comorbidities. During recent years several new agents are being tested, such as farnesyl transferase inhibitors (tipifarnib, lonafarnib), immunomodulatory drugs (lenalidomide, thalidomide), DNA methyltransferase inhibitors (5-azacitidine, decitabine), and histone deacetylase (HDAC) inhibitory drugs to ameliorate the poor prognosis of patients affected by this disease. We here report on a 70-year-old male, diagnosed as RAEB II in January 2002. Our patient received five of the above mentioned substances sequentially and responded to three of them. Now, 7 years later he is still alive and in good condition.

The patient was diagnosed as RAEB II in January 2002 and was transferred to our department in June 2002. Bone marrow puncture revealed a blast count of 10–15% and a normal karyotype. At that time he was transfusion-independent, but showed rapidly deteriorating platelet counts. The IPSS risk category was intermediate-II. Clinically, he suffered from fatigue, night sweat, and loss of weight. Secondary diagnoses were coronary heart disease, arrhythmia with atrial fibrillation, and a history of malignant melanoma of the temple (1997).

Before retiring, he worked at the chemical industry and had a history of benzene exposure; therefore, his bone marrow disease might be regarded as secondary MDS, which is often connected with an adverse course of disease, even though his karyotype was normal. At least, his pension insurance officially recognized the MDS as occupational disease. His father had suffered from esophageal cancer and his mother died of kidney cancer.

In July 2002, we initiated a therapy with thalidomide starting with 100 mg per day up to 400 mg per day. The treatment was poorly tolerated and had to be cancelled only 1 month later due to fatigue and drowsiness. A follow-up examination in September 2002 showed a stable disease with a still increased marrow blast count of 13%. Platelet count at that time had decreased to a minimum of 21,000/ $\mu$ l and hence we included him in a multicenter phase II trial with the farnesyl transferase inhibitor (FTI) tipifarnib [1]. Cell counts at start of treatment were: platelets 28,000/ $\mu$ l, Hb 11.1 g/dl, and ANC 700/ $\mu$ l. He started on a dosage of 600 mg p.o. per day. Already after two treatment cycles, he achieved a partial remission with improvement of peripheral cell counts and complete bone-marrow (BM) blast clearance (blast count, 3%). Maximum ANC was 1,900/ $\mu$ l, Hb 13.5 g/dl, and maximum platelet count was 263,000/ $\mu$ l. Between October 2002 and December 2004, he received 29 cycles of tipifarnib until the therapy was stopped due to polyneuropathy. At time of discontinuation, bone marrow examination revealed progression into RAEB I (BM blast count, 7%). The disease status remained stable and our patient did not develop transfusion dependency for about 1 year without further treatment. In October 2005, a progression into RAEB II occurred with a blast count of 12% and progressive thrombocytopenia was observed and consequently the patient was included in a multicenter study on the demethy-

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lating drug 5-azacitidine [2]. Peripheral cell counts at the initiation of therapy were: platelets 24,000/ $\mu\text{l}$ , Hb 11.1 g/dl, and ANC 500/ $\mu\text{l}$ . He obtained 7-day cycles with a dosage of 75 mg/m<sup>2</sup> for 7 days subcutaneously. Azacitidine induced a second marrow blast clearance, but with incomplete recovery of cell counts after 11 cycles in November 2006 (BM blast count, 3%). The ANC remained <1,000/ $\mu\text{l}$  and did not completely regenerate, a phenomenon frequently seen with azacitidine treatment, while hemoglobin increased to a maximum of 13.9 g/dl and maximum platelet count was 199,000/ $\mu\text{l}$ . The treatment was stopped in May 2007 after 15 cycles because of progressive disease (RAEB-I, 9% BM blast count). After discontinuation of the drug rapid transformation into AML occurred in June 2007 with a marrow blast count of 40–50%. At that time another experimental treatment with the HDAC inhibitor valproic acid was started (1,500 mg per day), but achieved no response. When after 2 months the platelet count further deteriorated we decided to treat the patient with decitabine dosed at 15 mg/m<sup>2</sup> intravenously every 8 h for 3 days. At the start of treatment platelet count was 18,000/ $\mu\text{l}$ , hemoglobin level was 10.3 g/dl, and ANC was 600/ $\mu\text{l}$ . Through this treatment he achieved a normal BM blast count (3%) for a third time after four cycles. Again, ANC remained relatively low, while hemoglobin and platelets again increased to 13.1 g/dl and 96,000/ $\mu\text{l}$ , respectively. The treatment is currently ongoing with a reduced dosage maintenance treatment (20 mg/m<sup>2</sup> once daily for 3 days). The bone marrow puncture in April 2008 revealed an increase in blast count to 20% which slightly decreased again in October 2008 to 12%. As the blasts exhibit CD33, a treatment with gemtuzumab ozogamicin could be beneficial in the future. Alternatively, a trial with clofarabine is currently being considered.

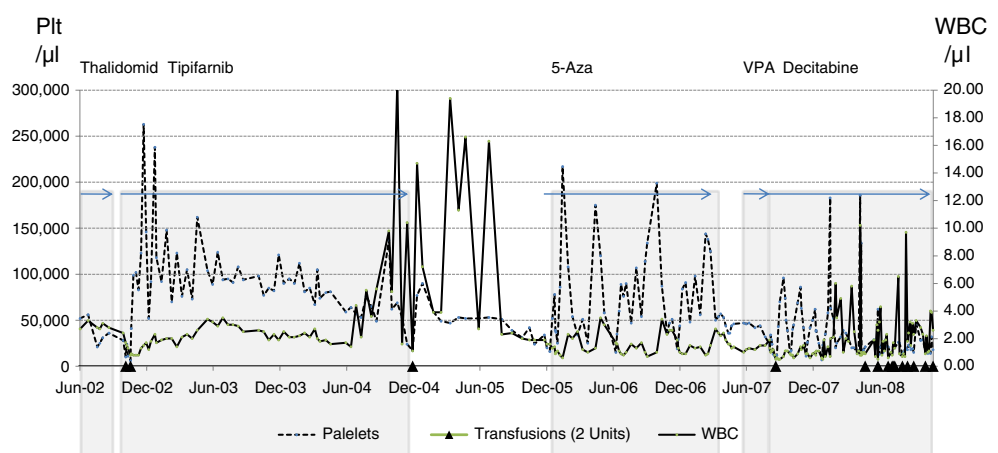
Throughout the whole period described the patient has received marrow examinations at regular, short intervals, as he was most of the time included within clinical studies. During this period the karyotype remained normal except

on one examination in November 2006 when a loss of the Y-chromosome was found in three metaphases. This alteration, however, was not observed again during follow-up. Even after normalization of marrow blasts a certain degree of dysplasia remained during all treatments, preventing the diagnosis of CR. Cell counts during the whole period described are depicted in Fig. 1.

Patients with higher risk MDS who are not suitable for intensive treatment approaches have a poor prognosis. Fortunately, several new drugs are under investigation, the first of which are already approved by the FDA. Our patient received several of these treatments sequentially and achieved repeated remissions, thereby exhibiting an unexpectedly long survival. Some of them, namely tipifarnib and 5-azacitidine, were given within the context of a clinical study, the other three drugs were given as individual treatment approaches. We started our therapy with thalidomide [3]. This substance belongs to the group of immuno-modulatory drugs which also includes lenalidomide. Both drugs exhibit a greater activity in low-risk MDS, and treatment with thalidomide, in contrast to its newer analog, is often complicated by grave side effects. For this our patient is a typical example. Since responses to thalidomide usually occur only after 2–3 months, its effectiveness is not evaluable in our case [4, 5].

FTIs were originally developed to inhibit the farnesylation of mutant, oncogenic Ras proteins, but the experience from clinical studies has shown that in vivo another currently unknown target must be responsible for responses to this drug [6, 7]. In different studies tipifarnib has exhibited an overall response rate in MDS patients of about 26–32% with a median response duration of 11.5 months, although complete remissions are rare [1, 8]. Our patient who responded for a duration of 29 months showed an exceptionally long response. Interestingly, the reason why tipifarnib had to be stopped in this case was polyneuropathy, which is not a common side effect of this drug. Possibly, this adverse effect only occurs after prolonged treatment.

**Fig. 1** Peripheral cell counts during the sequential therapies. The graphic shows well the myelosuppressive effects of tipifarnib, 5-azacitidine, and decitabine with widely alternating cell counts during treatment cycles especially regarding platelets



5-Azacitidine, a DNA methyltransferase inhibitor, was the first drug approved for MDS treatment in the USA in 2004. The multicenter study our patient participated in was conducted to confirm the promising data from previous US trials that had shown an overall response rate ranging between 40% and 47% [2, 9, 10]. The trial could not only confirm these response rates, but also demonstrate a significant survival benefit for the first time in MDS treatment [2]. Again, our patient is a good example for azacitidine treatment since it shows how improvements of peripheral blood parameters often only occur after prolonged therapy. A treatment alternative is the other demethylating agent decitabine, that although structurally related has demonstrated activity in patients after failure to respond to 5-azacitidine. Both drugs have different pharmacological properties, since decitabine is only incorporated into DNA whereas 5-azacitidine is mainly incorporated into RNA and only partly into DNA. Although the response duration in our case was short, we believe a trial of one demethylating drug after failure to the other is justified [11–15].

In between these two approaches the patient received a short unsuccessful trial of the HDAC inhibitory drug valproic acid. His failure to achieve a response is in line with data from a trial performed at our hospital on valproic acid showing responses preferably in patients with lower risk disease [16, 17].

Throughout the different therapies described our patient exhibited consistently a certain degree of dysplasia in the bone marrow as well as peripheral neutropenia, preventing a better response classification. This might be on the one hand evidence of the sustained application of drugs with a certain myelosuppressive effect. This phenomenon, for example, can sometimes be observed during treatment with imatinib as well. On the other hand, it is clearly also an expression of the lacking curative potential of most of the so-called targeted therapies. Still, some of them can prolong survival and improve quality of life and in some cases these new alternative treatment options can be used as a measure of bridging times to allogeneic transplantation or might also be interesting to use as maintenance treatment. With the new reduced intensity conditioning an increased number of patients have become candidates for allografting and the upcoming studies evaluating combined approaches with new drugs will likely further increase the number of patients eligible.

This case clearly demonstrates that some MDS patients achieve long-term benefits from investigational compounds and it is also a nice example of the progress made in MDS treatment during the last few years. Fortunately, this progress includes elderly patients, considered unfit for intensive approaches. The enrollment into clinical studies and other unconventional approaches should be taken into account whenever possible.

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