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Continued remission maintained with decitabine monotherapy in an elderly patient with *TP53* multi-hit acute myeloid leukemia relapsed after allogeneic transplantation

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Running head: DEC monotherapy in relapsed *TP53* mut AML after allo-HSCT

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Myeloid neoplasms with alteration of the *TP53* gene represent one of the greatest therapeutic challenges in hematology (and many other malignancies). Approximately 5-10% of newly-diagnosed acute myeloid leukemia (AML) cases present with this frequently fatal condition, even higher incidences are observed in secondary AML or treatment-related AML and older patients (17-30%)[1, 2] There is a strong association between *TP53* mutations and complex-monosomal karyotype in AML. This highly unfavorable combination results in an exceptionally poor prognosis, with a 3-year survival rate of 3% in some cohorts[3]. Current treatment strategies for younger and fit patients usually involve intensive chemotherapy followed by allogeneic stem cell transplantation (allo-HSCT)[4, 5]. Patients who are ineligible for intensive treatment are commonly treated with hypomethylating agents (HMAs) and venetoclax (VEN); however it was recently shown that the addition of VEN to HMA did not improve overall survival in *TP53* mutated AML[6, 7]. In the case of relapse after allo-HSCT there are no well-established therapeutic options which very often leads to a fatal outcome for these patients. Hence there is an urgent need for new therapeutic strategies to improve the outcomes of *TP53*-mutated AML. We share an instructive case of an elderly patient with *TP53*-mutated, secondary AML who achieved and maintained hematologic and molecular remission of relapsed AML after allogeneic stem cell transplantation by continued decitabine treatment. The patient consented to the use of biomaterial and publication of the results in scientific papers complying with established ethical standards.

In July 2020 a 72-year-old male presenting with leukopenia and anemia was diagnosed with sAML with myelodysplastic features by a hematologist in private practice. Bone marrow biopsy

showed an infiltration of 20% blasts. Molecular genetic testing revealed a *TP53* mutation (c.722C>G, p.Ser241Cys, VAF 20%) as a singular mutation detected in our diagnostic panel, compounded by the *TP53*/17p deletion (50%) detected by fluorescence in situ hybridization. The karyotype was highly complex (involving chromosomes 3, 5, 17, 20; see supplemental data for full karyotype) including an additional trisomy 21 and tetrasomy 22, chromosomal gains recurrently observed in multi-hit *TP53* disease [8]. We conducted a whole genome sequencing (WGS) analysis to confirm the complex karyotype and highlighted the numerical chromosomal aberrations as well as a subclonal deletion of chromosome 5q (del(5q)) (Figure 1). Initially, 6 cycles of subcutaneous azacitidine (AZA) were administered but did not achieve disease control. The patient was admitted to our hematological center (University Hospital Freiburg, Germany) for evaluation of an allogeneic stem cell transplantation. Before transplantation, bone marrow biopsy showed a blast persistence of 20%. In May 2021 transplantation was performed from an HLA-matched unrelated donor after conditioning with TFTreo (Thiotepa, Fludarabin, Treosulfan) reduced-toxicity conditioning (RIC), leading to complete hematological and molecular remission (first documented at day 30) with no signs of graft vs host disease (GvHD). Twelve months after transplantation, routine monitoring revealed mixed chimerism (1%, bone marrow) and increasing WT1 expression. Relapse treatment consisted of three donor-lymphocyte infusions (DLI) and one 3-day cycle of subcutaneous AZA, which had to be interrupted due to infectious complications. Following initial molecular relapse, the patient developed hematological relapse in September 2022 (30% bone marrow blasts) associated with a mixed chimerism of 43% (bone marrow) and renewed detection of the previously identified *TP53* mutation (VAF 34%) and *TP53*/17p deletion (45%). As a salvage therapy we immediately started 5-day decitabine (DEC) and VEN treatment. After two cycles of therapy the patient suffered severe hematological

toxicity requiring weekly transfusions as well as infectious complications (neutropenic fever). In November 2022, a bone marrow study showed blast persistence of 20% and the *TP53/*17p deletion in 40% of all interphase nuclei accompanied by a mixed chimerism of 21% (peripheral blood). Due to the lack of alternative treatment options and the previous hematological toxicity we continued therapy with DEC alone. Under this treatment the chimerism in peripheral blood slightly decreased to 14% by end of December 2022, followed by a good recovery of the blood counts without further need for transfusions. Moreover, after one year of outpatient DEC treatment with no major complications, a bone marrow study in November 2023 showed a reduced blast count of 2% and the absence of the *TP53*/17p deletion. By August 2024 peripheral leukocyte and thrombocyte counts had normalized while only mild anemia persisted and chimerism analysis in peripheral blood revealed complete donor chimerism (CC). Presently the patient is under maintenance treatment with 5-day DEC every 4-8 weeks (cumulative DEC treatment for 3.5 years, September 2022 – February 2026). Figure 2 summarizes the clinical course in relation to *TP53* mutational burden over time.

The positive outcome of the presented case allows us to discuss various aspects of *TP53*-mutated AML. The first point is the influence of the *TP53*-VAF on the outcome. Our patient showed an initial *TP53*-VAF of 20% and at relapse the highest VAF was 34 %. Short et al. demonstrated the superior OS (median OS 4.7 vs. 7.3 months) for patients with a *TP53* VAF <40%, although this effect could only be shown for patients who were treated with intensive chemotherapy (cytarabine-based) and not for HMA-treated patients[9]. Another study displayed an improved OS only for a 10%-VAF cut-off and did not find differences between different higher VAFs groups (10-22%, 22%-40%, >40%)[10]. Biologically there might be a rationale to

assume lower VAFs might indicate a less aggressive clone in the background; in this regard a lower VAF cut-off would be more intuitive but the exact cut-off that might reliably identify "lower risk" *TP53* mutated AML remains disputable.

Another unresolved question is whether DEC may be more effective than AZA in *TP53*-mutated AML. In a prospective comparison of the two agents in the ASTRAL-1 trail, no significant difference was observed in the *TP53* mutated subgroup[11]. However, some data suggests that a more intensive 10-day DEC regimen might have a beneficial effect in *TP53* mutated AML [12-14] Another interesting aspect is whether the sequence of DEC and AZA has an impact on the outcome. However, no conclusive data is available on this aspect to date. Further clinical studies on these issues are therefore of the highest interest.

DLI infusion combined with HMA is by now a well-established therapy in relapse after allo-HSCT and can induce deep remissions[15, 16]. Our patient did not respond to this strategy and was therefore exposed to DEC/VEN. The BCL-2 inhibitor VEN can enhance NK cell and T-cell activity and thus theoretically support the graft-vs-leukemia (GvL) effects in this situation[17, 18]. Still after two cycles of DEC/VEN the patient had disease persistence with 20% blasts in the bone marrow. The need for treatment de-escalation to DEC single-agent at this moment was not very promising at first sight due to the loss of anti-leukemic, T-cell and NK-enhancing effect of VEN[17, 18]. Nevertheless, the patient achieved an excellent response following this strategy, imposing the question what led to this at first glance surprising turn of events. In a setting of newly diagnosed AML, late responders to DEC/VEN have previously been described (24% of all CR were reached after ≥ 3 cycles)[19]. Secondly, we need to discuss the role of a VEN-induced hematological toxicity which could have impaired the GvL effect in our patient as recently

discussed by Mozaffari Jovein et al[15]. The importance of the GvL effect in the post-transplant setting can be crucial, which in this case might have been more important than the BCL-2-inhibition, and has possibly paved the way to remission.

Although the odds are unfavorable, we wish to emphasize not giving up on relapsed *TP53*-mutated AML patients. In some cases, deep remission is possible applying personalized strategies and factors like the GvL effect and late responders should be considered when making therapeutic decisions.

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FIGURE LEGEND

Figure 1: Results of WGS of bone marrow biopsy confirming the complex karyotype

(A) Circos plot showing the copy number alterations (CNAs) (losses in blue, gains in red, and diploid regions in black) and structural variants (green arcs) observed in WGS data.

(B) CNAs for chromosomes 5, 21 and 22 illustrating the subclonal 5q-deletion, trisomy 21 and tetrasomy 22.

Figure 2: *TP53* mutation burden of our index patient in correlation with clinical history

Figure 1

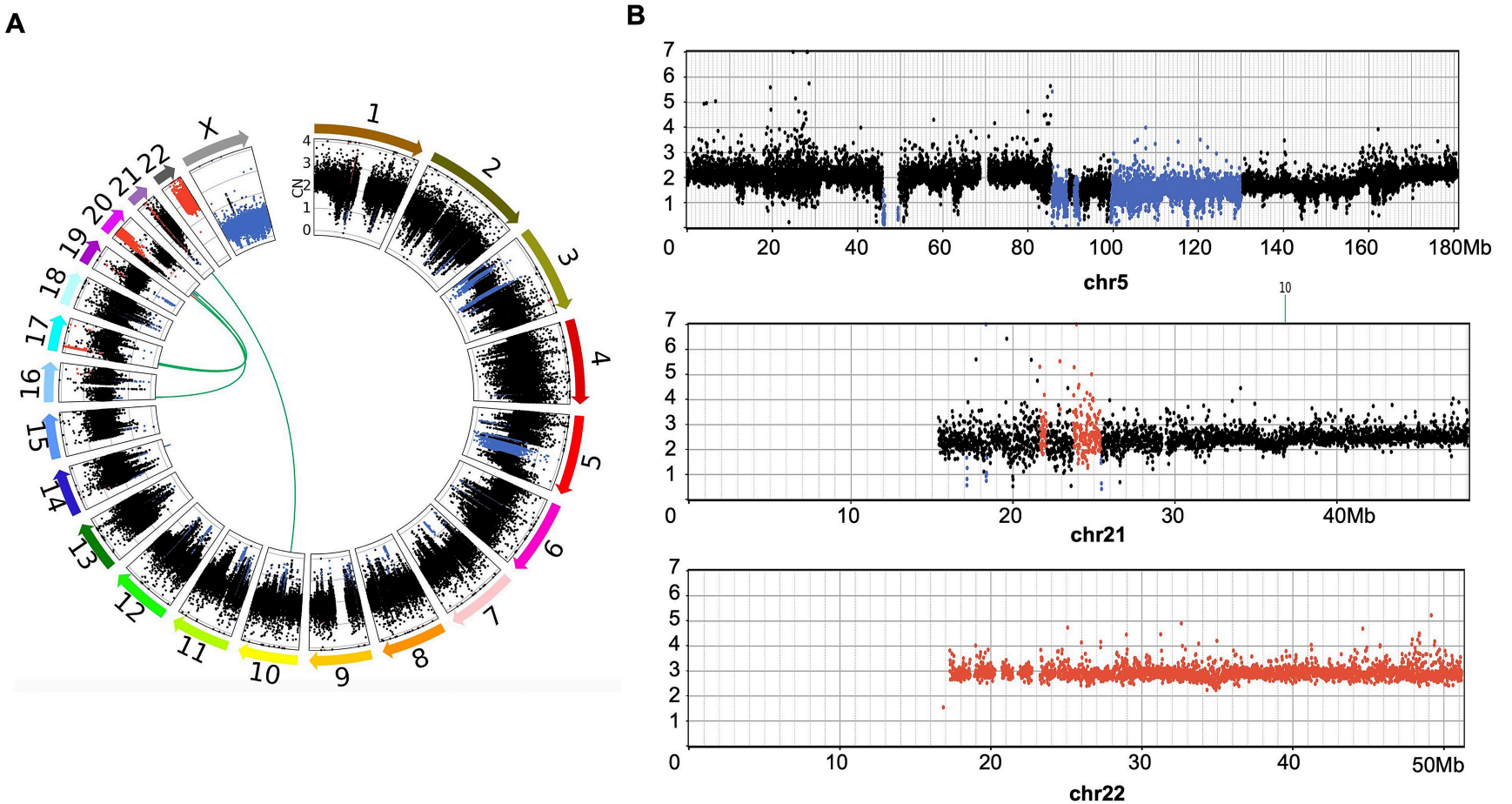
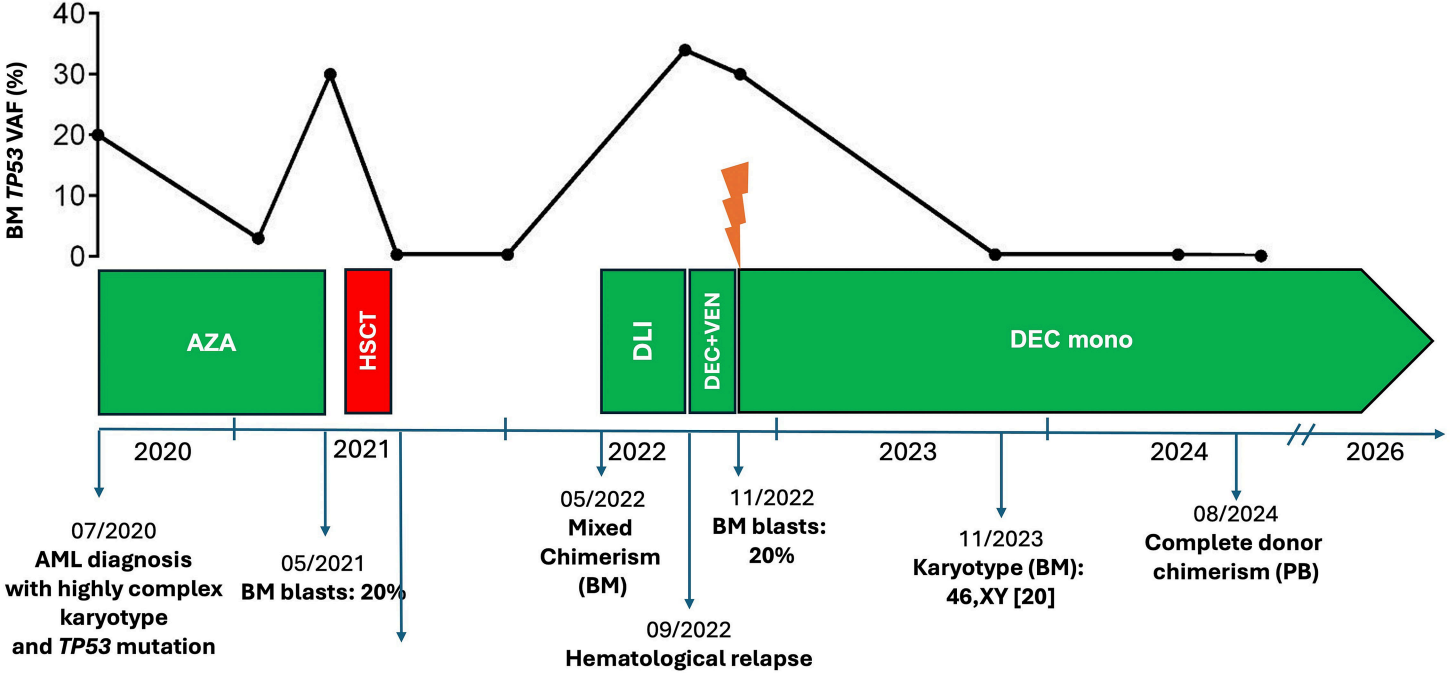

A
B
CN
chr5
chr21
chr22
10
20
30
40
50
60
80
100
120
140
160
180Mb
40Mb
50Mb

Figure 2


BM *TP53* VAF (%)
40
30
20
10
0
AZA
HSCT
DLI
DEC+VEN
DEC mono
2020
2021
2022
2023
2024
2026
07/2020
AML diagnosis with highly complex karyotype and *TP53* mutation
05/2021
BM blasts: 20%
05/2022
Mixed Chimerism (BM)
09/2022
Hematological relapse
11/2022
BM blasts: 20%
11/2023
Karyotype (BM): 46,XY [20]
08/2024
Complete donor chimerism (PB)