4. SPECIAL CONDITIONS

DIFFERENT OUTCOMES OF T(11;14) MULTIPLE MYELOMA AND THERAPY-RELATED ACUTE UNDIFFERENTIATED LEUKEMIA TO VENETOCLAX-BASED THERAPY AND ALLOGENEIC STEM CELL TRANSPLANTATION

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Background. Multiple myeloma (MM) is a clonal plasma cell (PC) malignancy characterized by biological heterogeneity. The presence of t(11;14) potentially predicts sensitivity to venetoclax (VEN). Secondary neoplasms represent a serious complication following exposure to alkylating agents. Acute undifferentiated leukemia (AUL) is a rare entity defined by the absence of lineage-specific differentiation. We report a case of MM and AUL treated with VEN-based therapy and allogeneic stem cell transplantation (alloSCT).

Case report. A 55-year-old man was diagnosed with IgG lambda MM in October 2021. Initial PET/CT revealed diffuse osteolytic involvement with multiple paramedullary masses. Laboratory evaluation showed elevated beta-2-microglobulin (7.57 mg/L) and monoclonal immunoglobulin (MIg) level of 29.77 g/L, while other biochemical parameters were within normal limits. Complete blood count demonstrated anemia (Hb 93g/L). Bone marrow (BM) assessment revealed up to 90% infiltration by PCs with an aberrant immunophenotype. Cytogenomic and molecular analyses identified t(11;14) and duplication of 1q21. The patient was treated with five cycles of VTD, achieving partial remission with a MIg level of 3.64 g/L and underwent high dose therapy (MEL200) with autologous stem cell support. He reached very good partial remission with a MIg level of 1.25 g/L and positivity of MRD at 0.06%. Lenalidomide was initiated as maintenance therapy, as no other option was available at that time. Two years later the patient was admitted for febrile neutropenia, and 63% of immature cells on blood smear. Flow cytometric analysis revealed 0.3% circulating PCs and 77% blast cells with a poorly differentiated immunophenotype: CD34+/CD45+/CD33+/CD7+/MPO-/cyCD3-/CD79a-, with partial expression of HLA-DR and EMA. Blast cell analyses demonstrated a complex karyotype, *TP53* and *TET2* mutation. Based on these findings, a diagnosis of AUL was established, while BM PCs accounted for only 0.2%, and the MIg level was 3.24 g/L. Given the adverse prognosis of AUL, the patient received induction therapy with VEN+HAM (cytarabine, mitoxantrone) achieving a morphologic leukemia-free state that was consolidated by VEN+AZA (azacitidine). This was followed by unresolving severe cytopenia. Pretransplant BM examination revealed no signs of AUL, persistent 1.6% PCs and morphological signs of hemophagocytosis. The patient underwent alloHSCT from a HLA-matched unrelated donor after reduced-intensity conditioning. At last follow-up, the patient remains in complete remission of AUL with 95.7% donor chimerism in BM. Despite treatment with VEN and alloSCT, there was no impact of this therapy on MM. BM examination revealed the presence of clonal PCs accompanied by continuous increase in MIg level to 15.96 g/L. The patient is currently under a close surveillance because of emerging MM relapse.

Conlcusions. Secondary malignancies in patients with MM are not uncommon. The development of *TET2*-mutated AUL may reflect therapy-induced leukemogenesis or expansion of clonal hematopoiesis under treatment pressure. Although VEN has demonstrated efficacy in t(11;14) MM, in this case the treatment was effective only against AUL. These findings highlight the need for careful long-term monitoring of patients for secondary malignancies. Furthermore, they underscore that the efficacy of targeted therapies may differ between coexisting hematologic neoplasms and the potential of immune dysregulation. *IGA_LF_2026_012*