Case Report

Early Death in Two Patients with Acute Promyelocytic Leukemia Presenting the bcr3 Isoform, FLT3-ITD Mutation, and Elevated WT1 Level

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1. Introduction

Early death (ED) in acute promyelocytic leukemia (APL) occurs in approximately 10 to 25 percent of patients within 30 days of starting induction chemotherapy and is frequently associated with severe hemorrhagic complications [1]. Although the addition of all-trans-retinoic acid (ATRA) to treatment regimens has considerably improved complete remission (CR) rates, the incidence of ED continues to be around 20% [2].

Elevated absolute blast and promyelocyte counts, high prothrombin time at presentation, thrombocytopenia, older age, and anemia have been reported as risk factors associated with ED in APL patients [3]. The aim of this report is to further clarify the clinical significance of molecular genetic parameters in the pathogenesis of hemorrhagic complications and ED in APL.

The PML-RARα transcript subtypes referred to as long (L or bcr-1), variant (V or bcr-2), and short (S or bcr-3), depending on the location of breakpoints within the PML site (intron 6, exon 6, and intron 3), have not been clearly associated with different prognosis or ED in APL [4].

Internal tandem duplication mutations of the fms-like tyrosine kinase-3 (FLT3-ITD) portend poor prognosis in acute leukemia and have recently been found capable of predicting ED in pediatric patients with acute APL [5]. Despite several reports of association between FLT3-ITD and other characteristics of APL, including elevated white blood cell (WBC) counts, hypogranular variant morphology (M3v), and the short (bcr-3) isoform of PML-RARα, the prognostic significance of FLT3 mutations still needs to be firmly established [6].

Wilms' tumor gene 1 (WT1), located on the short arm of chromosome 11, is expressed in most patients with acute myeloid leukemia (AML) or lymphocytic leukemia (ALL) [7]. APL represents the AML subtype with the highest WT1 expression levels. A recent study found that high WT1 mRNA expression correlated with the presence of FLT3 mutations, but whether this finding had an impact on clinical cure and/or outcome was unclear [8].
isoform bcr-3 and the FLT3-ITD mutation (Figure 1). The PCR was used to identify the presence of the PML-RAR fusion gene, presence of FLT3 ITD, and elevated WT1 expression (43679 copies).

The patient was diagnosed with APL (FAB M3v) and scheduled for treatment with the AIDA protocol, steroid prophylaxis, PLT, and fresh frozen plasma transfusions. After 48 hours of treatment with ATRA and one infusion of idarubicin, the WBC count rose to 57.7×10⁹/L, but headache worsened, becoming unresponsive to common pain relievers. Overnight the patient started vomiting and looked confused. Cranial computed tomography (CT) scans showed multiple bilateral supratentorial intraparenchymal hemorrhage, signs of diffuse cerebral edema, and moderate mass effect with compression of the right lateral ventricle. The patient was transferred to intensive care but died the following day.

3. Discussion

The problem of reducing ED in APL continues to baffle researchers worldwide and has become even more prominent in view of the marked improvement of CR rates since the introduction of combination induction therapy with ATRA and other innovative drugs such as arsenic trioxide (ATO). Although it is now possible for a vast majority of patients
to achieve durable CR, the risk of severe bleeding or ATRA syndrome remains a crucial aspect of APL management. The identification of risk factors associated to ED may help clinicians decide which patients need early and more intensive supportive and prophylactic care with high doses of steroids, PLT, and fresh frozen plasma transfusions and oxygen administration. Selected patients may also benefit from carefully monitored treatment with heparin or recombinant human soluble thrombomodulin [3].

The two clinical cases described here point to a peculiar and rapidly fatal form of APL, characterized by the contemporary presence of hypogranular morphology (M3v), short form (bcr-3) PML-RARα transcripts, FLT3-ITD mutation, and elevated WT1 expression.

Both patients presented high WBC counts at diagnosis. Investigation performed to establish whether the FAB subtype M3v had a higher ED rate because of hemorrhagic complications in comparison to the classical morphologic variant FAB M3 did not show any significant differences in outcomes after adjustment for WBC counts and/or relapse risk scores [10].

Some authors report that patients with the bcr-3 isoform appear to have a shorter disease-free and overall survival compared to patients with the bcr-1 isoform, independent of the initial leukocyte count [11]. Other authors associate the FLT3/IDT mutation with ED or relapse risk and suggest that patients carrying this mutation might benefit from treatment with FLT3 inhibitors in consideration of their potential ability to abrogate differentiation syndrome or coagulopathy [3, 4, 6].

Interestingly, our study indicates a possible role for WT1 overexpression as an additional risk factor for more aggressive APL. Indeed, a median value of 29590 WT1 copies has been reported in a cohort of 97 APL patients and higher values of WT1 have been associated to the presence of FLT3 mutation [8]. Both our patients had WT1 values above 40000 copies at diagnosis, suggesting that this parameter is a particularly important prognostic factor that needs to be promptly evaluated in all newly diagnosed cases of APL. However, further monitoring and study are warranted to refine the combination of risk factors associated with ED in APL.

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