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Case report 2

Successful management of transformed chronic myelomonocytic leukemia in a background of CKD in a resource poor setting

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Abstract

Chronic myelomonocytic leukemia (CMML), a myeloid neoplasm with features of both myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS), presents with peripheral blood (PB) monocytosis and has an inherent risk for transformation to acute myeloid leukemia (AML)[1,2]. Clonal cytogenetic changes are seen in around 30% of patients, while gene mutations are seen in >90% of patients[4]. Transformed AML shows a poor median overall survival (OS) and a modest survival advantage only with curative allogenic haemopoietic stem cell transplant (HSCT) [4]. We report here a patient with CMML, transformed to AML who achieved a good response with a hypomethylating agent (HMA). A 76-year-old man with multiple co-morbidities including stage 3B chronic kidney disease (CKD), was diagnosed with CMML with subdivision categories of myeloproliferative-CMML, CMML-1 and managed with hydroxyurea and supportive care. Three years after the initial diagnosis of CMML, he presented with acute blast transformation (BT) along with further deranged renal functions, compromised cardiac functions and early features of tumor lysis. He was successfully managed with subcutaneous (SC) azacitidine and achieved a good response even though he didn't reach true complete remission.

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Introduction

Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome/myeloproliferative overlap neoplasm characterized by persistent PB monocytosis and has an inherent risk for transformation to acute myeloid leukemia (15-30% over 3-5 years)[5,1,2]. The haematological and morphological features of CMML are heterogenous and vary from predominantly myelodysplastic to mainly myeloproliferative in nature. Myeloproliferative-CMML is commonly associated with activating RAS pathway mutations and adverse clinical outcomes. The identified risk factors include high risk karyotype, PB blast percentage, circulating immature myeloid cells, myeloid cells >10 x10^9/L, ASXL1, RUNX1, NRAS, SETBP1, DNMT3A and NPM1 mutations[5]. Post CMML-BT shows poor median overall survival of 6 months, with 1-,3-,5-year survival rates of 25%, 9%, and 6%, respectively. However, a modest survival benefit is observed from allogenic HSCT (5-year survival 21%)[3]. Post CMML-BT survival is negatively impacted by PB blast percentage, prior exposure to hypomethylating agents, high risk cytogenetics and failure to reach a complete remission/complete remission with incomplete recovery of counts with BT-directed therapies.

Case report

A 76-year-old male was referred in December 2019 from the medical clinic with elevated total white cell count and anaemia. Physical examination did

not reveal hepatosplenomegaly. He had multiple medical co-morbidities including long-term hypertension, history of a transient ischaemic attack in 2009, CKD stage 3B with an eGFR around 30-35mL/min/1.73m^2 (Serum creatinine 170µmol/L) and impaired cardiac functions with apical hypokinesia and diastolic dysfunction with preserved ejection fraction.

At presentation, he had a Hb of 8.2 g/dL, MCV 87fL, WBC 30.5x10^9/L, Neutrophils 19.9x10^9/L, lymphocytes 2.3x10^9/L, monocytes 6.35 x10^9/L (21%) and Platelets 309x10^9/L. Peripheral Blood film showed rouleaux formation, left shifted granulocytosis with dysplasia and monocytosis. Further investigations for evaluating secondary/reactive causes of monocytosis revealed only asymptomatic bacteriuria which resolved with antimicrobials. Although the follow up full blood count (FBC) showed reduced total WBC count in the range of 10-15x10^9/L with persistent monocytosis.

Bone marrow aspiration was performed and revealed hypercellular marrow for patient's age with markedly hypercellular granulopoiesis and increased monocytoid lineage cells mainly with mature monocytes. Dysplasia was noted in trilineage hematopoiesis including hypo-segmented nuclei, megaloblastoid forms, hypolobated and small megakaryocytes. Blasts were increased and accounted for around 9% of marrow nucleated cells, while the monocytes accounted for 10%. Cytogenetics showed normal male karyotype (46XY). Flowcytometry and molecular genetics were not available. The diagnosis of Myelodysplastic / Myeloproliferative neoplasm in the form of chronic myelomonocytic leukemia (CMML) was made. Given the percentage of bone marrow blasts been 9%, the patient was diagnosed as CMML-1. The MD Anderson pro-gnostic score (MDAPS) was 1- low risk category and CMML specific cytogenetic risk stratification (CPSS) was low risk (normal karyotype).

He was started on SC erythropoietin 10000IU/weekly considering the CKD background and the Hb improved and maintained around 10g/dL without any blood transfusions. The patient was regularly followed up with monitoring of counts. After a year the total WBC started to rise gradually along with a drop of Hb. Around 5% of blasts appeared in the PB along with a left shifted granulocytosis and monocytosis. He also complained of fatiguability. Therefore, hydroxyurea 500mg/daily (dose adjusted according to the renal insufficiency) was stared for cytoreduction and erythropoietin was increased to 30,000IU/weekly with infrequent blood transfusions. He responded partially and Hb response remained poor and needed frequent red cell transfusions. Other contributory causes for anaemia were excluded. Meanwhile his renal functions gradually deteriorated to CKD stage IV with the eGFR drop to 20mL/min/1.73m^2 (Serum Creatinine - 270µmol/L). He was monitored with FBC, blood pictures and renal functions monthly. The patient was closely followed up by the nephrology team and started on renal supportive medications.

Three years after the initial diagnosis he presented with rapidly rising counts, worsening anaemia and fatiguability in spite of the ongoing management with hydroxyurea and erythropoietin. His was pale with bilateral pitting ankle edema but there was no hepatosplenomegaly.

Full blood count (FBC) showed WBC 116.1x10^9/L, Blasts 45%, Neutrophil 23%, Monocytes 15%, Lymphocytes 10%, Eosinophils 6%, Hb 6g/dL and Platelets 590x10^9/L. Peripheral Blood film showed 45% of medium sized blasts with increased nuclear/cytoplasmic ratio, moderately dispersed chromatin, 1 to 3 nucleoli, some containing cytoplasmic granules and occasional blasts containing Auer rods resembling myeloblasts, marked neutrophil leukocytosis with left shifted maturation and dysplasia, monocytosis and platelet anisocytosis.

A repeat bone marrow was performed and revealed markedly hypercellular marrow for the patient's age with 30% myeloblasts, markedly hypercellular granulopoiesis with all stages of maturation, hypercellular megakaryopoiesis and suppressed erythropoiesis. Tri-lineage haematopoiesis showed dysplasia. Blasts were Sudan BlackB positive. Trephine biopsy showed few focal areas of mildly increased fibrosis with reticulin staining of grade 0 to 1. Therefore, the diagnosis of CMML transformed into AML was made according

to morphology. Bone marrow flowcytometry, cytogenetics and myeloid mutation studies were unavailable due to resource constraints.

Renal functions further deteriorated with the serum creatinine 345µmol/L (19% increment from the most recent baseline), Blood Urea 19.5mmol/L, and eGFR of 14mL/min/1.73m^2. Also, the uric acid level was elevated (517µmol/L) indicating possible early tumor lysis. However the rest of the biochemical markers of tumor lysis were negative and ECG showed sinus rhythm with old ischemic changes and no arrhythmias.

Given the background of multiple co-morbidities and worsening organ functions, he was not a suitable candidate for intensive chemotherapy or curative allogeneic HCT. Hence, the patient was started on SC azacitidine 100mg daily for 5 days, in the first five days of 28 days cycle after pre-treatment evaluation. The azacitidine regimen of 100mg/m^2 for 5 days was selected locally to minimize drug wastage as well as to minimize the number of hospital visits. Pre-emptive measures were taken to minimize the risk of tumor lysis syndrome including hydration, allopurinol (dose adjusted in accordance with renal insufficiency, 100mg daily). Renal functions, electrolytes and other parameters of tumor lysis were closely monitored (Table 1) and Renal supportive medications were continued. The Hb level was maintained around 8g/dL with blood transfusions and weekly erythropoietin 30,000IU. Adverse events experienced by the patient during the first cycle were mild nausea with one episode of vomiting in spite of anti-emetic premedication, mild erythema and slight discomfort at the injection site, mild headache and insomnia.

The management was multidisciplinary with inputs from nephrology and medical teams in optimising organ functions.

Seven cycle of SC Azacitidine were continued. Even though the patient did not achieve a complete remission, the total WBC count dropped gradually with reduced blast count and improvement of renal functions to previous baseline. The Hb response remained poor needing regular blood transfusion

Table 1. Trends of the investigations during cycle 1 of SC Azacitidine

Azacitidine – cycle 1	**Day 1**	**Day 7**	**Day 25**
FBC			
Total WBC- 109/L	148.6	92.3	84.4
Granulocytes%	29	30	44
Lymphocytes%	10	9	13
Monocytes%	18	16	15
Blasts%	40	41	25
Hb-g/dL	7.9	8.0	8.7
Platelets – 10^9/L	680	303	401
Serum Creatinine – µmol/L	345	331	287
Potassium – mmol/L	4.2	4.8	4.0
Uric acid – mmol/L	517 (high)	584 (high)	332.3 (normal)
Calcium – mmol/L	2.3	2.26	2.33
Phosphorous – mg/dL	4.85	3.9	3.8

although the frequency was improved from weekly to once in three weeks. The serum ferritin levels remained less than 1000 nmol/L.

Table 2. Response of the blast count in PB to SC Azacitidine

FBC	End of 3rd cycle	End of 6th cycle
Total WBC (x10^9/L)	40.8	14.6
Granulocytes %	53	65
Monocytes %	20	12
Blasts %	15	5

During the 4th cycle of SC azacitidine, he complained central chest pain with dynamic ischaemic ECG changes and borderline positive troponin I and managed as myocardial infarction, NYHA type 2 due to anaemia. Therefore, haemoglobin was maintained above 8g/dL in subsequent azacitidine cycles.

Unfortunately, SC azacitidine was stopped after the 7th cycle due to the unavailability of the drug and patient is currently on the best supportive care.

Discussion

Chronic myelomonocytic leukemia (CMML) is the most common MDS/MPN, which is characterized by sustained PB monocytosis, dysplasia and various somatic mutations. CMML occurs in the background of clonal hematopoiesis, with TET2 and SRSF2 mutations being early initiating events. The subsequent acquisitions of ASXL1, RUNX1, SF3B1 and DNMT3A mutations usually give rise to dysplastic CMML, while ASXL1, JAK2V617F and RAS pathway mutations give rise to proliferative CMML[5].

Diagnosis is according to World Health Organisation (WHO) diagnostic criteria for CMML[2]. Blood and bone marrow monocytes often have aberrant phenotype. Flowcytometry with CD11b, CD13 and CD16 is useful in diagnosing CMML[2].

Two subdivisions with striking clinical and genetic features are now formally recognized in the upcoming 5th edition of the (WHO) Classification of Haemato-lymphoid Tumours[1]. The subtyping is based on WBC: myelodysplastic CMML (MD-CMML) (WBC < 13 ×10^9/L) and myeloproliferative CMML (MP-CMML) (WBC ≥ 13 ×10^9/L)[1]. In addition, CMML is classically sub grouped based on the percentage of blasts and promonocytes in the bone marrow and peripheral blood, into CMML-1 (< 5% in blood, < 10% in the bone marrow) and CMML-2 (5 to 19% in the blood; 10 to 19% in the bone marrow, or less if Auer inclusions are present)[1,2]. CMML-0 (<2% blasts in blood and <5% blasts in bone marrow) is no longer a subgroup of CMML as it does not provide prognostic significance[1].

In our case, the diagnosis was mainly based on morphological evaluation due to the resource poor setting. He was subtyped under myeloproliferative CMML because the initial presentation was with leukocytosis and persistent monocytosis without reactive/secondary causes and he was subcategorized into CMML-1 according to the blast percentages.

Clonal cytogenetic abnormalities are seen in around 30% of CMML patients. Common alterations include trisomy 8, -Y, abnormalities of chromosome 7 (monosomy 7 and del7q), trisomy 21 and complex karyotypes[4,5]. CMML specific cytogenetic risk stratification system (CPSS) has been developed to predict 5year OS. Our patient showed normal male karyotype at diagnosis and was categorized into low-risk category with 5-year OS of 35%. In further prognostication, the MD Anderson prognostic system (MDAPS) is CMML-specific and identified a hemoglobin level <12 g/dL, presence of circulating immature myeloid cells (myelocytes, promyelocytes and metamyelocytes), absolute lymphocyte count >2.5x10^9/L and ≥10% bone marrow blasts as independent predictors for inferior survival[4,3]. Our patient had one point and belonged to low-risk category. Therefore, he was initially observed without any CMML-directed therapies with regular blood count monitoring and supportive care with erythropoietin. Later, due to persistent high WBC, hydroxyurea was started to

control blood counts and proliferative features with rising counts as there are some data to support proliferative CMML, leukocytosis/monocytosis can be associated with increased lysozyme levels leading to renal damage (lysozyme nephropathy). Although HMAs such as 5-azacitidine, decitabine, and oral decitabine with cedazuridine (cytidine deaminase inhibitor) remain US FDA approved agents for the management of CMML, its usage affects adversely for future treatments[5]. Furthermore, the overall response rates (ORR) ranging from 40% to 50% and true complete remission rates being <20%. ASXL1 mutations predicted a lower ORR, whereas the ASXL1 wild type/TET2mutate genotype was associated with higher CR rates[5].

Despite therapy, there is 15-30% of post CMML transforming to acute myeloid leukemia within 3-5 years. This transformed AML is associated with an adverse outcome compared to de novo disease. Allogeneic HSCT remains the only curative option for patients with CMML. However, due to the advanced median age at diagnosis and existing comorbidities, this is an option to a small fraction of patients as CMML is associated with aging (approximately 10%). Standard induction chemotherapy followed by allogeneic HSCT should be considered for all eligible patients as post CMML-BT carry dismal outcome. Previous treatment with HMA affects adversely[5].

Our patient progressed to post CMML-BT three years after the initial diagnosis of CMML and he was not eligible for transplant due to advanced age and multiple co-morbidities. Since he was not previously treated with HMA, SC azacitidine was started as a non-intensive option. Although azacitidine carries a lower tumor lysis risk, he was at high risk of tumor lysis due to AML with high WBC and already impaired renal functions which further deteriorated with the disease transformation. However, he was successfully managed and achieved a good response. The median survival of the HSCT ineligible group who received HMA was 4.3 months, with most patients dying from co-morbidities, primary induction failure or disease relapse[5]. Our patient achieved good response with HMA and maintained a longer response at the end of 6 months. A contributory factor for longer survival could be no prior introduction of the HMA before the CMML-BT which affects adversely[5,2].

Authorship

All authors contributed equally.

Authors declare no conflicts of interest.

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