中文題目：Ruxolitinib 治療對帶有 CSF3R T618I 突變之慢性嗜中性白血病無效，但可改善骨髓纖維化：個案報告

英文題目：Chronic neutrophilic leukemia with CSF3R T618I mutation is refractory to ruxolitinib therapy , but with improvement of myelofibrosis : A case report

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Introduction

Chronic neutrophilic leukemia had its revised diagnostic criteria made by World Health Organization in 2016, the presence of CSF3RT618I or other activating CSF3R mutation is one of major criteria, and was recognized as a driver mutation. Ruxolitinib, the Janus kinase Inhibitor (*JAK* inhibitor), was found effective in treating CNL in some case reports. Here, we present a case of CSF3RT618I mutation CNL patient , who is not responsive to Ruxolitinib treatment in his hemogram, however, the bone marrow fibrosis was improved.

Case report

A sixty-five-year-old man presented with dyspnea and exercise intolerance for 1 month. Body weight lost 7 kg in recent 8 months. The hemogram showed anemia(6.0 g/dL), hyperleukocytosis (131890/mm^3) and thrombocytopenia (131000/mm^3). WBC differential count showed Band = 3.0%, Seg = 69.0%, Blast = 2.0%, Promyelocyte = 2.0%, Myelocyte = 2.0%, Metamyelocyte = 7.0%, Monocyte = 10.0%, Lymphocyte = 5.0%, no eosinophil or basophils in Aug 2018. The initial impression was CMMoL of myelodysplasia syndrome, as bcr-abl is not detected by RT-PCR. We treated him with azacytidine x 5 course , without improvement. Subsequent bone marrow study revealed increased myeloid to erythroid ratio (from 5:1 to >10:1) and grade 1 myelofibrosis were noted. In the mean time , the NGS Genetic study of peripheral blood found Colony-Stimulating Factor 3 Receptor (CSF3R) T618I mutation, allele frequency = 47.2%. We gave him with Ruxolitinib according to reference data(1) . But we didn't see obvious response. He still need regular blood transfusion , and leukocytosis persistent. The third time bone marrow biopsy was done after Ruxolitinib treatment for 4 months, which still showed hypercellular marrow with increased myeloid component. Comparing to 2nd round of bone marrow biopsy, hypercellularity(95%) and myeloid to erythroid ratio(10:1) remained unchanged. However, previous finding of myelofibrosis was no longer detected in this study.

We also send peripheral blood for NGS study , and there remains same T618I mutation with similar allele frequency.

Discussion

1. In our case, we firstly treated the patient as CMMoL due to the rarity of CNL and lack of genetic profile. However, after applying Azacytidine therapy for 5 cycles, we found not only hyperleukocytosis continued , the thrombocytopenia and anemia also worsen.
2. Second, after the treatment with Ruxolitinib, 2nd round of NGS analysis revealed the same allele frequency of CSF3R T618I mutation, showing that the burden of the oncogenic driver is not reduced under treatment with Ruxolitinib.
3. From literature review, the myelofibrosis is a poor prognosis factor of CNL. We found the Ruxolitinib might have the power of withheld marrow fibrosis.

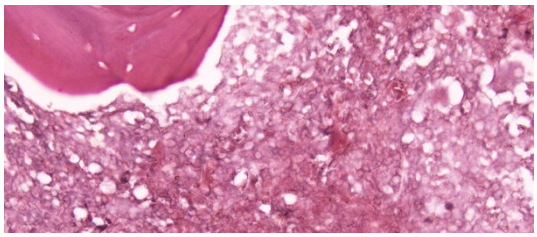

Fig.1 The initial bone marrow study , no fibrosis of reticulum stain

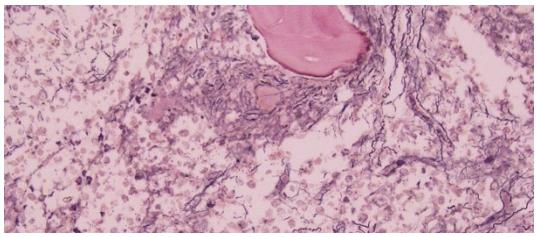

Fig.2 Five months after azacytidine therapy, marrow showed the grade 1 fibrosis in reticulum stain

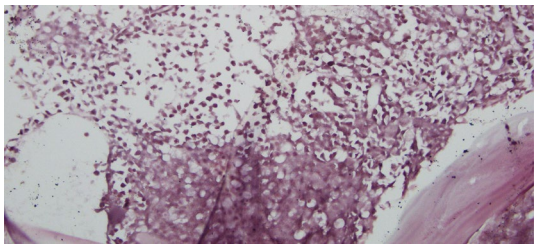

Fig.3 Four months after Ruxolitinib therapy , no marrow fibrosis noted.

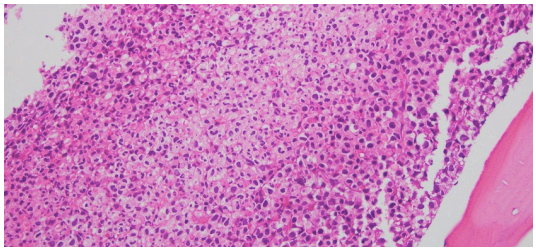

Fig.4 Hypercellular marrow persistent despite Ruxolitinib therapy

Conclusion

We reported this case to highlight the rarity of chronic neutrophilic leukemia and the possible treatment options. Although recent discovery of CSF3R mutation and its related pathway has made treatment with the JAK inhibitor an viable option, our case was refractory to Ruxolitinib despite adequate mutation was detected. Mutation allele frequency was also remained unchanged in follow up NGS study, which may related to lack of selective anti-clonal or disease modifying effect from Ruxolitinib. However, regression of myelofibrosis was found in this patient after Ruxolitinib treatment, which can be an advantage since myelofibrosis is a poor prognosis factor to CNL. Further investigation of other driver mutation to CNL and other JAK inhibiting agents combined with anti-clonal effect were both warranted based on findings from our case.