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CORRESPONDENCE

De Novo JAK2 V617 F Positive AML: The Picture is Getting Clearer

Kanjaksha Ghosh[1] · **Kinjalka Ghosh**[2]

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To:

The Editor;

JAK2 mutation has been traditionally detected in myeloproliferative disorders specially in polycythaemia vera [1].

Recently we came across an interesting paper by Anvardi et al. on JAK2 V617 F positive AML both as a de novo variant and as evolution of different myeloproliferative neoplasms (MPN) [2].

JAK2 V617 F mutation is traditionally a mutation of MPNs specially of polycythaemia vera. Hence presence of this mutation in a case of AML evolving from MPN may not be unusual though this is not always the case [3]. De novo AML due to JAK2 mutation is appearing in literature from 2005 onwards [4]. Mostly as case reports or as small case series.

Our group was one of the early investigators who reported certain characteristics of this de novo AML with peculiar blast morphology showing swiss cheese nuclei and prominent Golgi system coupled with substantial number of dead cells probably related to Golgi-endoplasmic protein stress and hypolobated megakaryocytes with relatively less number of blasts and total leucocyte count in peripheral blood compared to similar de novo AML with wild type of JAK2 gene. This neoplasm also showed combined CD 19 and CD 56 positivity (In addition to myeloid marker positivity and CD34 negativity) in the back ground of FLT3 ITD mutation and t (8,21) cytogenetic change. Complex karyotypic changes were not seen and these patients responded poorly to standard 3 + 7 therapy for induction. This type of AML constituted 2.3% of all AML [5]. We considered these AML to be a distinct biologic entity, a premise which is now confirmed by the present much more exhaustive study with changes in large number of genes studied through modern NGS technology showing distinct molecular signature compared to MPN evolving into AML. Clinically inconsequential splenomegaly was an important observation. Ding et al. [6] observed in a one year old child with this kind of AML significant thrombocythaemia during recovery from induction chemotherapy and felt that this could be an important clue for the presence of this mutation if it was not detected or suspected initially.

The paper by Aynardi et al. [2] confirmed many of our findings however their study is retrospective in nature hence needs to be confirmed through a prospective and properly blinded methodology.

STAT-3 pathway was shown to be activated in a large number of AML patients even without detectable JAK2 mutation [7] however the details of this mechanism is not understood. The present study as well as the study presented by Pappaemmanuil et al. [8] showed with the help of NGS technology that in addition to one or two driver mutations, each AML patients harbor quite a few other mutations with different activities on gene regulation and expression. These individual genetic and epigenetic changes may alter the morphology, immunophenotype, natural history and response to drugs for each of the individual patients necessitating precision genomic medicines in individual cases.

The question is whether use of targeted therapy against JAK2 mutation like ruxolitinib alone or with combination chemotherapy and/or immunotherapy will be effective in

✉ Kanjaksha Ghosh
kanjakshaghosh@hotmail.com

[1] Haematology and Transfusion Medicine, Surat Raktadan Kendra & Research Centre, Surat, India

[2] Clinical Biochemistry, Tata Cancer Centre, Ernest Borges Road, Mumbai, India

this condition cannot be answered without a good clinical trial. Actually this subset of AML is relatively rare i.e. $< 5\%$ of all AML so we will need a large multicentric study to get adequate accrual of such patients within reasonable time frame. To achieve that end efforts should be made to form a collaborative platform wherein these entities could be treated in a common way so that we may even have a case series confirming or disproving a hypothesis.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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