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Identifying Myeloma Patients at Risk of Lenalidomide or Pomalidomide Resistance at Relapse: A New Opportunity

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Gooding et al reported an interesting study that demonstrated the presence of acquired genetic changes in cereblon in patients with multiple myeloma refractory to lenalidomide or pomalidomide.[1] We provide a short summary and appraisal of this study and implications for clinical practice.

Background

Cereblon (CRBN) is a crucial component of the E3 ubiquitin ligase complex and marks substrate proteins for proteolysis. Binding of lenalidomide (Len) or pomalidomide (Pom) to CRBN leads to proteolysis of Ikaros family zinc finger 1 (IKZF1) and IKZF3, leading to myeloma cell death.[2]

Brief Summary of This Study

This was an in-vitro study, in which DNA and RNA extracted from CD138 enriched plasma cells and peripheral blood germline DNA were collected at baseline and relapse in patients with multiple myeloma (MM). These cells were analyzed using whole genome sequencing and RNA sequencing to obtain germline and tumor data with a focus on *CRBN*. Significant findings included the definition of several mutations in *CRBN*, broadly classified as point mutations, copy number losses, and a distinct exon-10-deleted variant. Overall frequency of mutations was noted to progressively increase with subsequent lines of treatment, being 0.9% in newly diagnosed multiple myeloma to 2.2% in Len refractory and 9% in Pom refractory patients. Strikingly, structural variation or loss of CRBN expression was noted in 8% of Len refractory and 24% of Pom refractory patients. A novel exon-10-deleted *CRBN* transcript was defined, which leads to deletion of the Len/Pom binding region on CRBN. Frequency of exon-10-deleted CRBN was noted in 20% of Len refractory and 29% of Pom refractory patients. Patients who were Len refractory and had CRBN alterations had a significant reduction in progression free and overall survival compared with those without any changes. This is the first study that illustrates *acquired mutations* in target proteins leading to immunomodulatory drug (IMiD) resistance, independent of *CRBN* gene expression.

Relevance

The current study has significant implications for routine treatment of MM and represents another step in individualizing therapy at the time of relapse. The central role played by CRBN in mediating IMiD activity previously led to conjecture that quantitative or qualitative CRBN alterations can mediate responses to therapy with Len/Pom. Patients who have a high expression of CRBN demonstrate better responses to Len.[3] Conversely, patients with very low expression of CRBN show no response to a Len/Dex combination.[4] The weight of evidence so far points at a quantitative reduction in the expression of CRBN as the crucial step in mediating drug resistance.[5] Other qualitative changes in CRBN, that is, mutations in CRBN pathway and downstream proteins have been found to be infrequent, even in patients with clinical resistance to Len/Pom.[6] It was suggested that CRBN function may be altered with other mechanisms including epigenetic and posttranscriptional changes.[7] Despite this data, a role of CRBN expression in identifying patients at risk of clinical resistance has not been proven.[8,9]

The present study impacts both the above paradigms and has implications for the near future. The prognostic impact of mutations in this study is independent of *CRBN* gene expression, and may annul the results of previous studies that largely relied on quantitative *CRBN* expression. Myeloma is associated with a nearly 100% risk of relapse, and selection of appropriate therapy at relapse improves progression free and overall survival.[10] This study provides a potential mechanism for utilizing *CRBN* mutations as predictors of IMiD responsiveness. As mutations in *CRBN* occur more frequently

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at disease progression, a clinical algorithm may be devised, with a plan to document *CRBN* mutations at the first instance of progression in Len/Pom exposed patients. Identification of mutations that preclude a response will allow selection of alternate effective agents. Treatment of myeloma is already set to become "personalized" based on baseline genetic profile, and this study provides a guidepost at the time of first relapse.[11]

There appear to be two major hurdles before this clinical model can be adopted for regular use. First, a large multicenter database of commonly occurring CRBN mutations and their association with drug resistance and clinical outcomes must be defined, and only those predicting for high rates of drug resistance (80–90%) must influence a change in therapy. Second, the best method for examining CRBN mutations is still contentious. Most studies have used DNA and RNA extracted from CD38+ plasma cells for the evaluation of *CRBN* mutations, but several variations exist. *CRBN* mutations can be tested by targeted polymerase chain reaction, gene sequencing, or next-generation sequencing techniques. The present study used whole genome sequencing, which may not be universally available. Several methodological variables like the source of MM cells, method of purification, and identification of altered splice variants of CRBN must be harmonized so that a common protocol can be used.[8]

Identification of mutations in CRBN is a great first step in identification of patients at risk of resistance to Len/Pom at relapse. Future studies would need to evaluate the association of CRBN modifications with geographical variations and disease presentation. A model similar to tyrosine kinase mutations in chronic myeloid leukemia at disease progression can be envisioned and may prove to be a first step in personalized medicine at relapse in myeloma.

Conflict of Interest

None declared.

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