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Commentary

Role of Genetic Mutations in Treating Multiple Myeloma Patients

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DESCRIPTION

Multiple myeloma in general is called as the "cancer of plasma cells". The plasma cells that are usually found in the bone marrow are an important part of the immune system which work together to fight infections and other diseases. Multiple myeloma features leads to low blood counts due to the overgrowth of plasma cells in the bone marrow [1]. Due to low blood count, it leads to anemia which makes the people weak and fatigued. This disease can also lead to thrombocytopenia causing increased brushing and bleeding. Multiple myeloma also leads to bone and calcium problems by interfering with the cells that are responsible to keep the bones strong. It leads to other diseases like kidney problems, infections, monoclonal gammopathy, smoldering multiple myeloma, solitary plasmacytomas, waldenstorm macroglobulinemia.

There are certain genes which play important roles in pathogenesis, progression and prognosis of MM which include KRAS, NRAS, TP53, FAM46C, DIS3, BRA, p53, etc. Among all the genes KRAS was the common mutated gene and FAM46C was the least mutated gene. Mutation diversity affects different nodes of the signal network and is an essential feature of myeloma [2]. Multiple gene mutations (KRAS, NRAS and BRAF) have been found in the same patient, with mutation of different genes located in the same pathway. Studies have found that FAM46C and DIS3 are likely to be the driver genes of MM. Other studies have found that BRAF, TRAF3, CYLD and RB1 are involved in the pathogenesis of MM. The identification of such driver gene mutations in MM has brought great hope to the field of personalized medicine. Patients with a unique set of mutations can now receive appropriate targeted therapy [3].

Among all the genes present, the presence of p53 mutations within exons 5 to 9 of the p53 gene was investigated by PCR amplification of each exon and subsequent SSCP analysis in non-denaturing polyacrylamide gel electrophoresis. Because the percentage of malignant plasma cells may vary greatly in pathologic samples taken from MM patients, the samples containing a sufficient number of malignant cells to detect Ig gene rearrangements by Southern blot analysis. To assess the sensitivity of SSCP method, DNA from a T-cell line carrying a known p53 mutation (Jurkat-heterozygous for codon 196, exon 6) was serially diluted with normal DNA; each dilution was then amplified for exon 6 of p53 and analyzed by SSCP.

Targeted sequencing analysis revealed that KRAS was the most common mutated gene, followed by NRAS, TP53, DIS3 and FAM46C. Initial treatment for MM is generally the induction of high- quality remission, including complete response. Still, there's recurrence in nearly all patients, which is best explained by the presence of tumor clonal heterogeneity at the time of diagnosis, with differential sensitivity to different drugs leading to clonal selection and elaboration [4]. Successful treatment requires the targeting of a wide range of targets including tiny subclones. Thus, it's necessary to watch the gene changes of the tumor cell population under the pressure of treatment selection to estimate the efficacity. The role of CRBN, IKZF1 and IKZF3 in treatment with immune modulators and XBP1s and IRE1 in treatment with proteasome inhibitors have helped in understanding the disorders such as MM which further emphasizes the importance of personalized treatment [5]. The integration of MM cytogenetics and gene mutations can be used to enhance MM division, track clonal changes, induce a more accurate prognostic and guide treatment more effectively.

The spectrum of mutants identified in recent studies is inadequate to define their role and place in the personalized treatment of MM. It isn't yet clear whether medicines that target these mutational changes will produce a meaningful or lasting response in patients.

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