MultipleMyelomaHub

General MM

The evolutionary history of MM correlates with outcome and could help tailor therapy

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The concept of neutral tumor evolution moves away from the classic Darwinian model of changing clonal dominance, and instead, in this model, clones with distinct mutational profiles can exist for longer periods of time. The tumor-driving mutations are thought to have arisen in the first malignant cell, with subsequent tumor evolution considered neutral and responsible for intra-tumor heterogeneity. In order to better understand the clonal evolution of Multiple Myeloma (MM), and the prognostic impact for patients, a study was carried out by David C. Johnson from the Division of Molecular Pathology at The Institute of Cancer Research, Sutton, UK, along with numerous collaborators, and published in Blood in August 2017.

Results:

- Whole Exome Sequencing (WES) of tumors was carried out in order to assess mutant allele frequency distributions, using two independent cohorts of patients (pts) that had received immunomodulatory drugs (IMiDs):
    - Myeloma XI study: 333 pts; CoMMpass Study: 434 pts
- Proportion of tumors in which neutral evolution was found:
- Myeloma XI trial = 65/333 (20%); CoMMpass study = 74/434 (17%)
- Neutral evolution was unaffected by age, sex or International Staging System (ISS) grade
- Tumors with IGH translocations had a greater propensity towards neutral evolution than hyperdiploidic tumors, as shown by R^2 values:
    - Myeloma XI = 0.963 *vs* 0.956 ($P = 0.002$); CoMMpass = 0.957 vs 0.947 ($P = 0.034$)
- IGH translocations are hypothesized to bring about earlier mutational events, providing increased 'tumor fitness' compared with hyperdiploidy and relative independence from microenvironmental factors
- Patients (pts) receiving non-intensive therapy (neutral *vs* non-neutral tumors):
    - Median PFS: Myeloma XI = 15.6 *vs* 20.5 months ($P = 0.019$); CoMMpass = 18.7 *vs* 28.1 months ($P = 0.036$)
    - Overall Survival (OS): Myeloma XI = 27.3 *vs* 49.6 months ($P < 0.001$); CoMMpass = 21.3 months *vs* not reached ($P = 0.029$)
- No significant differences were observed for pts receiving intensive therapy (high-dose melphalan and ASCT)
- The prognostic potential of neutral evolution was independent of ISS, adverse IGH translocations, 1q gain, and TP53 deletion

Conclusion:

Using 767 MM patients from two different treatment cohorts, almost a fifth of MM tumors were found have neutral evolutionary dynamics. This was also found to correlate with a lower PFS and OS in patients receiving iMiDs, and was attributed to reduced efficacy in these patients due to less influence on external factors. The use of such genetic analyses to further understand the evolutionary history of MM in a given patient could help to steer more tailored therapy, as well as providing further insight towards predicting patient outcome.

Abstract

Recent studies suggest that the evolutionary history of a cancer is important in forecasting clinical outlook. To gain insight into the clonal dynamics of multiple myeloma (MM) and its possible influence on patient outcome we analysed whole exome sequencing tumor data for 333 patients from Myeloma XI, a UK phase III trial and 434 patients from the CoMMpass study, all of which had received immunomodulatory therapy (IMiD). By analysing mutant allele frequency distributions in tumors we found that 17-20% of MM is under neutral evolutionary dynamics. These tumors are associated with poorer patient survival in non-intensively treated patients, consistent with reduced therapeutic efficacy of micro-environment modulating IMiD drugs. Our findings provide evidence that knowledge of the evolutionary history of MM has relevance for predicting patient outcome and personalising therapy.

References

1. Johnson DC. et al. Neutral tumor evolution in myeloma is associated with poor prognosis. Blood. 2017 Aug 21. pii: blood-2016-11-750612. DOI: 10.1182/blood-2016-11-750612. [Epub ahead of print]