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Multiple myeloma - Section 2

Genetic classification of myeloma for prognostication and treatment selection

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Take-home messages

- Genetic analyses at the time of diagnosis, and probably first relapse, are mandatory in MM to define the prognosis.
- Genetic abnormalities in MM are used to predict prognosis and currently, most of the prognostic genetic changes identify patients with high risk
- The mutational landscape in MM, mainly based on whole exome sequencing, have confirmed the genetic heterogeneity of MM, with no specific common mutation
- The genetic profile information could be used to propose specific drug targeted combinations although this is still a matter of debate.

Introduction

Multiple myeloma (MM) is a very heterogeneous disease, clinically, biologically, and genetically. In contrast to non-Hodgkin's lymphomas, in which genetic and immunophenotypic characteristics define clear sub-entities, we so far failed to define different diseases in MM. Several attempts have been proposed, the most recognized classification is based on genetic abnormalities. However, such classifications do not clearly identify subgroups of patients with a different biology and outcome.

State of the art

In MM, genetic abnormalities have been mainly used to predict prognosis (Table 1). Currently, most of the prognostic genetic changes identify patients with high risk, i.e., short progression free survival (PFS) and overall survival (OS). The first and most important abnormalities are the loss of part of the short arm of chromosome 17, known as del(17p), and the translocation t(4;14) both identifying a high risk subgroup of about 20% of the patients. More recently, other abnormalities have been also described to be associated with a poor outcome, loss of the 1p32 region, and to a lesser degree, gains of 1q. In contrast, almost no good risk abnormalities have been identified, except hyperdiploidy, which represents probably a heterogeneous subgroup.

Very recently, several publications reported the mutational landscape in MM. Mainly based on whole exome sequencing, these studies confirmed the genetic heterogeneity of MM, with no specific common mutation, two mutations seen in ~ 20% of the patients (KRAS and NRAS), and the others observed in less than 10% of the patients. These mutations did not enable the definition of specific subclasses. Of note, none of these mutations display a specific poor or good outcome.

Could we use these abnormalities to design specific treatment approaches? This question has been addressed by several trials, focusing on the outcome of patients with high risk features, however, data are not clear-cut. If the combination of lenalidomide with dexamethasone (len-dex) is clearly not the best choice for high risk patients, the association of a third drug seems to improve their outcome at the time of relapse. This has been first suggested in the ASPIRE trial (len-dex +/- carfilzomib). In the experimental arm, high risk patients (del(17p) and/or t(4;14)) presented a much longer PFS. This has been confirmed in the TOURMALINE 1 trial (len-dex +/- ixazomib). Similar data have been described with monoclonal antibodies, first in the ELOQUENT 2 trial (len-dex +/- elotuzumab), and recently in the POLLUX trial (len-dex +/- daratumumab). However, all these trials did not define the high risk in the same way, especially in the cutoff for del(17p) assessment. Furthermore, all these trials were dedicated for relapsed patients, and no data is currently available in the frontline setting.

Finally, could we use the mutational analyses to propose targeted therapies, as currently performed for solid tumors? Few

mutations are really 'drugable'. Only one report described the use of vemurafenib (a BRAF inhibitor) in a patient with relapsed MM and a specific V600E BRAF mutation. This patient responded dramatically. But this is a single case report, and this mutation is present in only 3-5% of the patients.

Future perspectives and conclusions

Genetic analyses at the time of diagnosis, and probably first relapse, are mandatory in MM to define the prognosis. Whether this information can be used to propose specific drug combinations is a matter of debate. Current data are suggesting that high risk patients may benefit from triplet combinations. The future of targeted therapies in MM is undefined, but probably rather obscure due to the low mutational profile and clonal heterogeneous evolution observed in most MM patients.

Table 1. Main genetic abnormalities with poor prognosis in MM.

Deletion del(17p)
Translocation t(4;14)
Loss of 1p32 region
Gains of 1q
Non hyperdiploidy

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