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General AML

ISAL 2019 | A multi-stage prognostication tool for acute myeloid leukemia

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On February 25, 2019, Moritz Gerstung from the European Bioinformatics Institute, Cambridge, UK, presented at the Acute Leukemias XVII Biology and Treatment Strategies biennial symposium, in Munich, Germany, on the topic of prognostic approaches to acute myeloid leukemia (AML).

The genetic spectrum of AML is complex. In a study by Elli Papaemmanuil *et al.*, published in the *New England Journal of Medicine*, 2016, the research team identified 5234 driver mutations across 76 genes or genomic regions, that may be involved in leukemogenesis. The study identified 1062 separate mutation combinations, as well as 11 subtypes of AML. This genetic diversity makes it difficult to determine the impact that each variant has on the patient outcome but does enable the researchers to understand heterogeneity in patient responses.

Multi-stage prognostication tool

Utilizing the genetic information and data by Moritz Gerstung *et al.*, published in *Nature Genetics*, 2017, a multi-stage prognostication tool was developed, using a cohort of 1540 patients. The patient outcomes were reported as follows:

- Induction (N = 1540)
  - Lost to follow-up (n = 7)
  - Non-remission death (n = 264)
- Complete remission (n = 1269)
  - Cure (n = 489)
  - Non-relapse death (n = 165)
- Relapse (n = 615)
  - Salvage (n = 140)
  - Relapse death (n = 475)

When including over 200 predictor variables, it was possible to determine an individual patient's prognostics, based on the genetic landscape of their disease. Without applying any information on genetics or risk factors, the average patient progresses through disease in the order listed above. When specific genetic factors are included, it is possible to see the percentage increase or decrease in risk of each outcome.

In patients with a *TP53* mutation alone:

- Patients achieving complete remission: 20% reduction
- Non-remission death: 50% increase
- Non-relapse death: 25% increase
- Patients relapsing: 50% increase
- Relapse death: 20% increase

When looking at a *TP53* mutation in combination with a complex karyotype:

- Patients achieving complete remission: 30% decrease
- Non-remission death: 150% increase
- Non-relapse death: 42% increase
- Patients relapsing: 76% increase
- Relapse death: 50%
- Overall survival very poor in this population

NPM1 mutation alone:

- Patients achieving complete remission: 65% increase
- Non-remission death: 20% increase
- Non-relapse death: 10% decrease
- Patients relapsing: 50% decrease
- Relapse death: 5% decrease
- *NPM1* mutation conferred a higher rate of remission and more favorable survival

The figures highlighted above show that the likelihood of each outcome may vary between patient groups, and that comparing a multitude of the output graphs can identify chemo-resistant, relapse-prone and benign groups.

When compared to the European LeukemiaNet (ELN) classification (2011) the outcomes provided by the multi-stage prognostication model proved to be similar. However, the ELN system uses fewer variables, therefore it is unable to capture as much variation within individual patients.

The multi-stage prognostication model was cross-validated with other trials, as well as other data sets and a letter to *Blood* which identified that this model outperformed the ELN stratification.

This tool is available as an online calculator, which can be accessed here.

Predicting treatment outcome

It is possible to use this to investigate the effects of different treatments in individual patient scenarios. For clinicians debating the choice of therapy, such as whether allogeneic hematopoietic stem cell transplant at first relapse is the most suitable option for an individual patient, this may provide invaluable insight. In some scenarios, the tool has predicted a better response to an alternative therapy compared to the ELN suggested treatment, potentially paving the way for personalized treatment plans.

Further development

This tool is also being utilized in myeloproliferative neoplasms (MPN). Driver genes have been identified that are involved in the transformation from chronic to myelofibrosis - the genetics of MPN are predictive of progression, but not survival. In these cases, the tool has identified that preventing progression of the disease is a key factor. The group are also working on a prediction tool for myelodysplastic syndromes.

By using the multi-stage prognostication tool, it is possible to input detailed patient information and receive accurate predictions of treatment outcomes. Moritz Gerstung highlighted the importance of continually updating the database, in order to for the data to be current and valid.

References

1. Gerstung M. Genetic landscape of AML and its relevance for treatment. ACUTE LEUKEMIAS XVII Biology and Treatment Strategies Meeting, Munich, DE.