COMMENTARY

Measurable residual disease in childhood B-cell acute lymphoblastic leukemia

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In a recent report in *Nature Cell Biology* (2022. 24:242–52) Zhang and coworkers discuss comparative genetic and biochemical features of leukemia cells from children with B-cell acute lymphoblastic leukemia (ALL) obtained at diagnosis, in remission, and at relapse.¹ The authors analyzed large numbers of single-cell transcriptomes looking for dynamic changes and simultaneously, B-cell receptor sequences. They report that in contrast to leukemia cells at diagnosis, those at relapse shifted to a poorly-differentiated state. Changes in residual leukemia cells in remission were more complicated. Differential functional analyses highlighted activation of the hypoxia pathway in residual leukemia cells which correlated with drug resistance which was reversible with appropriate drug interventions in in vitro and in vivo models. The authors suggest this might be a therapy approach to eradicating measurable residual disease (MRD) in childhood B-ALL.

This is a data dense article which requires understanding a machine learning algorithm. I suggest putting aside at least 5 hours to read and understand the text and supplement. I had to read it twice. This is not something to breeze through while texting on WeChat if you really want to understand the authors’ message and to critique it appropriately.

First, a word on nomenclature. The authors use the term minimal residual disease. As John Goldman and I discussed several years ago the correct term is measurable residual disease.² Minimal is a subjective term; minimal to 1 person is not necessarily minimal to another. What we are considering is what can and cannot be measured in someone in complete histological remission. (Another source of confusion; remissions are not measurable in someone in complete histological remission. (Another source of confusion; remissions are not measurable in someone in complete histological remission.)³ How residual leukemia cells escape eradication (or if chemotherapy selects for emergence of hypoxic cells) we would need a prospective study showing a correlation. This article does not provide such data but perhaps the authors have this as their next task. This would be a difficult study to do since we unfortunately cure most children with B-cell ALL. Another difficult challenge would be to prove anti-hypoxemic drugs improve therapy outcomes.

Another interesting question is how we cure children with B-cell ALL. Most children achieving a histological remission with conventional therapy with corticosteroids, vincristine, cytarabine, doxorubicin, L-asparaginase, and etoposide then receive 2 to 3 years of so-called maintenance therapy with 6-mercaptopurine and methotrexate. But what exactly does maintenance therapy do? It is most unlikely these drugs typically given at low doses kill ALL stem cells. More likely, B-cells, normal and leukemia, are fated to die and maintenance therapy simply delays leukemia relapse sufficiently so these cells commit suicide.²

I was especially interested in the authors’ use of a machine learning algorithm to classify stages of B-cell development (described in METHODS). For those unfamiliar with this technique this is a supervised approach where there are learning and validation cohorts. Reproducibility was high but correct attribution accuracy always depends on accuracy of labeling of the training dataset.

In summary, I recommend a careful reading of this important study. Much of the methods will be beyond the comfort zone of most hematologists. As such, struggling through and trying to understand the techniques may be as or more important than the conclusion. If you are going to print the article out (a good idea for reading on the high speed train) be sure to use a color printer or you will be lost. Finally, this article is a striking example of the increasingly high quality of biomedical research.

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in China. I congratulate the authors. I wish they had submitted it to Leukemia.

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REFERENCES

[1] Zhang Y, Wang S, Zhang J, et al. Elucidating minimal residual disease of paediatric B-cell acute lymphoblastic leukaemia by single-cell analysis. Nat Cell Biol 2022;242–252.

[2] Goldman JM, Gale RP. What does MRD in leukemia really mean? Leukemia 2014;28:1131.

[3] Orwell G. Politic and the English Language. London: Sahara Publisher Books; 1946.

[4] Hourigan CS, Gale RP, Gormley NJ, Ossenkoppele GJ, Walter RB. Measurable residual disease testing in acute myeloid leukaemia. Leukemia 2017;31:1482–1490.

[5] Yang S, Kay NE, Shi M, Ossenkoppele G, Walter RB, Gale RP. Measurable residual disease testing in chronic lymphocytic leukaemia: hype, hope neither or both? Leukemia 2021;35:3364–3370.

[6] Othus M, Gale RP, Hourigan CS, Walter RB. Statistics and measurable residual disease (MRD) testing: uses and abuses in hematopoietic cell transplantation. Bone Marrow Transplant 2020;55:843–850.

[7] Goldman J, Gordon M. Why do chronic myelogenous leukemia stem cells survive allogeneic stem cell transplantation or imatinib: does it really matter? Leuk Lymphoma 2006;47:1–7.

[8] Houshmand M, Simonetti G, Circosta P, et al. Chronic myeloid leukemia stem cells. Leukemia 2019;33:1543–1556.

[9] Gale RP, Butturini A. Maintenance chemotherapy and cure of childhood acute lymphoblastic leukaemia. Lancet 1991;338:1315–1318.