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General AML

Does ABCG2 overexpression in AML cause resistance to deoxyadenosine analogues?

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At the end of July 2017, the AGP reported the results from the phase II randomized study which compared the safety and efficacy of idarubicin and cytarabine combined with nucleoside analogues clofarabine (CIA) or fludarabine (FIA) in newly diagnosed Acute Myeloid Leukemia (AML) patients and was published in Cancer by Elias Jabbour *et al.* from The University of Texas MD Anderson Cancer Center.. The results from this study showed that both clofarabine and fludarabine were associated with high complete remission (CR) rates and a 2-year overall survival (OS) rate higher than 50% and that, in comparison with treatment with idarubicin and cytarabine alone, FIA was associated with superior outcomes for younger AML patients.[1]

In a subsequent correspondence by Mario Tiribelli and colleagues published in Cancer, in October 2017, it was suggested that despite these promising results, potential disease relapse is still the major cause of poor long term outcomes for AML patients. Overexpression of ATP-binding cassette subfamily G member 2 (ABCG2), a multi-drug resistance protein, is associated with higher rates of failure to achieve remission and leads to shorter disease-free survival. Additionally, previous findings have shown that FIA-based regimens fail to overcome the effects of ABCG2 levels on disease relapse. Thus, Tiribelli *et al.* investigated the possible influence of ABCG2 on CIA and FIA activity *in vitro*.[2]

Tiribelli *et al.* demonstrated that overexpression of ABCG2 impacted the toxicity of FIA and CIA thus mediating resistance to these nucleoside analogues. Tiribelli *et al.* concluded that their findings confirmed a potential role of drug efflux pumps, particularly ABCG2, overexpressed by AML blasts, as a cause of resistance to CIA and FIA. They concluded by suggesting that ABCG2 levels should be assessed at diagnosis and at reoccurrence as ABCG2-negative patients are more likely to benefit maximally from CIA and FIA. [2]

Elias Jabbour *et al.* responded to the findings by Tiribelli *et al.* in a correspondence published in the same issue of Cancer, regarding the role of ABCG2 in AML. They reported that the main studies which investigated the role of ABCG2 pumps have varied in their estimation of the proportion of newly diagnosed AML patients with high levels of ABCG2 to cause resistance. Jabbour *et al.* however accepted that ABCG2 may have mediated resistance to FIA and CIA in their phase II study at least in the subset of patients with ABCG2 overexpression.

Jabbour *et al.* suggested that younger AML patients with chemosensitive disease may benefit from the evaluation of drug efflux pump expression strategies and targeting those transporters. For those who do not fit into this group, the authors advocated novel agents and combination therapy, for example the addition of FMS-like tyrosine kinase 3 (FLT3) inhibitors to chemotherapy. In conclusion, the authors noted that continued molecular classification of AML will be required in order to make improvements in AML outcomes.

References

1. Jabbour E. *et al.* A randomized phase 2 study of idarubicin and cytarabine with clofarabine or fludarabine in patients with newly diagnosed acute myeloid leukemia. Cancer. 2017 Apr 20. DOI: 10.1002/cncr.30883.

2. Tiribelli M. *et al.* ABCG2 overexpression and deoxyadenosine analogue activity in acute myeloid leukemia. Cancer. 2017 Oct 20. DOI: 10.1002/cncr.31037

3. Jabbour E. *et al.* Reply to ABCG2 overexpression and deoxyadenosine analogue activity in acute myeloid leukemia. Cancer. 2017 Oct 20. DOI: 10.1002/cncr.31036