Where does the combination of venetoclax with decitabine or azacitidine or LDAC fit in the treatment paradigm for AML?

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Hi, welcome to *Managing AML*. I am Dr. Brian Jonas. I am frequently asked, "In 2020, the FDA approved venetoclax in combination with decitabine, or azacitidine, or low-dose cytarabine (which is what low-DAC stands for). Where does this new combination fit in the treatment paradigm for AML?"

I think this is a great question. Now that the combination is approved for patients who are 75 or older, or unfit for chemotherapy, this is really the standard of care now for this population. By this I mean any of these three combinations: venetoclax in combination with decitabine; or a combination of azacitidine; or a combination of low-dose cytarabine. When I encounter a new patient with AML, newly diagnosed, untreated, who's 75 or older, I automatically consider one of these combinations for that patient.

Now, there's also patients who are less than 75 years old that are considered unfit for induction that would also be candidates for these regimens based on the FDA label. Those might include patients with poor performance status, patients with abnormal kidney function, or abnormal lung function, or liver function. This is based on the VIALE-A trial, as well as the VIALE-C trial, which was for low-dose cytarabine, where they used a modified version of the Ferrara criteria[1] for determining eligibility of those less than 75.

Now, there's also some potential off-label use of this combination and this is supported, for example, by the NCCN guidelines, and in particular patients who are under 75 who have poor-risk cytogenetics who may not be a candidate for other therapies such as FLT3 inhibitors or CPX-351. If they don't have an indication for that and they have poor-risk cytogenetics, then the HMA or low-dose cytarabine combinations with venetoclax are a potential option for those patients. At least, based on guidelines, and many of us in practice agree with those guidelines. That would be another area where this might fit in.

I think what's going to be really interesting over the next few years is to see whether or not clinical trials are going to suggest the use of these combinations. Perhaps even in younger patients or fit patients even. There's been a long-standing question about whether the 7+3 regimen, which has been standard of care for 40-something years, is really the best thing for patients. It's very toxic and doesn't always work. Perhaps a lower intensity regimen that has

similar response rates might be able to provide adequate disease control, and certainly, keep patients more fit with less toxicity during these inductions and may be better transplant candidates. Be on the lookout for additional clinical trials that are actually starting to compare the new combinations with the old 7+3 backbone.

In addition, some really interesting new trials are going to take these combinations that are now approved, as I mentioned, for older patients, and adding third drugs to them, so-called triplet therapies, which might be explored in certain mutational subgroups, or cytogenetic subgroups, or other subpopulations of AML, where perhaps the addition of the third drug, assuming it's not too toxic, can potentially advance the outcomes with these combinations.

I think those are some really exciting areas that are going to evolve over the next few years, and so I'm looking forward to seeing that. Currently, I would say these regimens are best used in the patients who are 75 or older, or those unfit for induction chemotherapy, and like I said, maybe some patients who are also younger with adverse or cytogenetics are possible candidates for this regimen as well.

Reference:

1. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia*. 2013;27(5):997-999. https://www.nature.com/articles/leu2012303