Therapy focus - Hopes rise for a breakthrough in leukaemia logjam

Robin Davison

2016 might finally see some tangible progress in acute myeloid leukaemia, a notoriously difficult indication where the "7+3" chemotherapy regimen of cytarabine and daunorubicin has held sway for 40 years as the frontline standard of care.

That progress will almost certainly come in the form of Novartis's midostaurin, which has shown a survival advantage in combination with standard of care in the subset of AML patients harbouring FLT-3 mutations. However, improvements could also come from Celator Pharmaceuticals, which is poised to report results from its pivotal study with Vyxeos, a liposomal reformulation of 7+3 (see table below).

Breaking through

In December, Novartis reported results from the phase III Ratify trial of midostaurin, showing a 23% improvement in overall survival. The project subsequently gained breakthrough therapy designation, and given Novartis's plan to file in the first half it could see approval towards the end of this year.

Meanwhile, Celator last week confirmed that its phase III trial, named 301, had reached the number of events required to trigger an overall survival analysis, and that results would become available before the end of March.

Unusually, the 301 study has already rendered a positive result for a key secondary endpoint, induction response rate, where last year Celator reported a 14-point improvement, with 47.7% of patients on Vyxeos achieving a complete response with or without platelet recovery, versus 33.3% for conventional 7+3 (Celator could quietly break leukaemia record, June 25, 2015). The US microcap obviously hopes that this will translate into a survival advantage.

Celator's study enrolled patients aged 60 to 75 with secondary AML – those whose disease arose as a result of myelodysplastic syndromes or was related to prior therapy for another cancer type. This is a subgroup with few treatment options.

This choice of setting was driven partly by ethical constraints as Celator could not treat younger, de novo AML patients – who can tolerate 7+3 – when it was not known whether its therapy was superior. Nevertheless, if the 301 study establishes Vyxeos as superior to 7+3 in secondary AML, physicians would likely extrapolate its use to de novo patients in preference to the conventional regimen.

Volasertib and sapacitabine

Two other phase III AML studies are due to report this year, both in the front-line setting in older patients. These are the Polo-AML-2 trial of Boehringer Ingelheim’s volasertib, and the now almost forgotten Seamless study of Cyclacel’s sapacitabine.

Cyclacel’s failed an interim analysis for futility last year, but unusually the DSMB still recommended its continuation to a conclusion. Hopes are therefore very low, but Seamless might possibly suggest that equivalence or non-inferiority, and Cyclacel might claim a benefit thanks to its less IV infusion-heavy dosing schedule. However, it would still have to go before the regulators on bended knee.

One company that is already doing this is Sunesis, which has filed vosaroxin in Europe in relapsed/refractory AML, despite its Valor study missing its primary endpoint in 2014. The filing is for the sub-population of patients over 60 years old, and Sunesis thinks the EMA is willing to be generous in its interpretation of the rules, given the lack of alternatives.

There is some precedent for this, with the EMA’s approval of Dacogen for elderly patients with AML in 2012. The FDA, however, declined to consider this approach last year.

As well as Novartis's midostaurin, in the past month a second agent, AbbVie and Roche's venetoclax, received
breakthrough therapy designation - in combination with hypomethylating agents as front-line therapy for elderly patients with AML, where it is in phase I.

Eight other agents are in phase III for AML, according to an analysis by EP Vantage. This group is expected to be joined by MEI Pharma’s pracinostat and Seattle Genetics’ vadastuximab talirine later this year.

MEI plans to study its HDAC inhibitor in combination with Vidaza in elderly, front-line AML, pitching it in the same space as volasertib and Otsuka’s decitabine follow-up, guadecitabine. Meanwhile, Seattle plans a study to investigate its ADC in combination with hypomethylating agents in older AML patients.

Given that AML has been a pharmaceutical development graveyard for so long, it would be heartening to see some of the pivotal readouts and some progress in the field.

This story has been amended to correct the combination drug in the planned pracinostat study.

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