Evaluate Vantage

February 13, 2012

Therapeutic focus - Drugmakers brush off failure and keep trying in AML

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The failure of Dacogen to gain a new indication in acute myeloid leukaemia from the FDA is another letdown in the ongoing quest to bring new medicines to bear on the challenging blood cancer. Chemotherapy remains the chief first-line treatment to induce remission of the dysfunctional white blood cells; but with an older and sicker patient population this is frequently not a viable option, making the search for targeted medications with more tolerable side effects an urgent one (*Dacogen looking to Europe following initial US disappointment, February 10, 2012*).

Teva's Trisenox is the only branded drug licensed for first line use in AML, and only in a subset of patients; the remainder are utilised for maintenance therapy following chemotherapy. Vidaza is authorised in Europe for certain AML patients, although any US use is strictly off-label. Thus there remains hope that candidates such as Sunesis Pharmaceuticals' Vosaroxin, Novartis' PKC482 and Cyclacel Pharmaceuticals' CYC682 could soon offer physicians and patients new options (see table).

Abnormal cells

Acute myeloid leukaemia is a disease of the bone marrow; abnormal myeloblasts, the precursor to white blood cells, are formed as a result of genetic mutations. These fill the blood marrow and impede development of properly functioning blood cells. Symptoms include anaemia, frequent infections and easy bleeding or bruising.

Chemotherpy with cytarabine and idarubicin, azacitidine, or cytarabine, daunorubicin and cyclosporine are typical regimens aimed at inducing remission. As a sign of how little progress there has been in the space, the leading branded seller in AML is Neupogen, Amgen's colony stimulating factor used to treat symptomatic neutropaenia, used in conjunction with chemotherapy. As with most cancers, AML is a disease with many subtypes, and as such the targeted drugs on the market have narrow uses.

Celgene's Vidaza is authorised in those AML patients whose disease has progressed from myelodysplastic syndrome and have only 20-30% abnormal blood cells. Trisenox, or arsenic trioxide, which came to Teva with its acquisition of Cephalon, is used only in acute promyelocytic leukemia to induce and maintain remission. After an appeal to regulators, Meda's Ceplene was granted European authorisation, but has been sent back for more trials in the US, with a call for a two-arm trial to demonstrate efficacy; its current use is with interleukin as a maintenance therapy following a first remission, and is only used in patients younger than 60.

Such a demand for further trials are not surprising given that Pfizer's Mylotarg was withdrawn from the market after confirmatory trials failed. However, with so few options for such a larger number of patients – a majority of older patients may not be able to withstand even a first round of standard-dose chemotherapy - and therefore with low dose treatment the only option, it might not take much to prove efficacy in those patients.

Those that have failed to just that, however, include Astex's Dacogen, already used in myelodysplastic disorders, Seattle Genetics' lintuzumab and Antisoma's AS1411 and AS1413 (*Seattle Genetics brushes off lintuzumab trial and focuses on brentuximab vedotin, September 14, 2010*).

Selected late stage AML pipeline

	Product	Generic Name	Company	Pharmacological Class	Proprietary Level 2	2
Filed	Dacogen	decitabine	Johnson & Johnson*/Eisai**/Astex Pharmaceuticals***	DNA methyltransferase (DNMT) inhibitor	NME + Orphan Drug	9

Phase III	Vosaroxin	vosaroxin	Sunesis Pharmaceuticals/Dainippon Sumitomo Pharma***	Naphthyridine analogue	NME	-
	PKC412	midostaurin	Novartis	Signal transduction inhibitor	NDA	-
	CYC682	sapacitabine	Daiichi Sankyo/Cyclacel Pharmaceuticals***	Pyrimidine analogue	NME	-
	Elacyt/CP-4055	elacytarabine	Clavis Pharma	Pyrimidine analogue	NDA + Orphan Drug	-
	Onrigin	laromustine	Nanotherapeutics/Yale University***	Alkylating agent	NME	-
	Treosulfan medac	treosulfan	medac	Bifunctional alkylating agent	New Derivative	-
	OMS0728	tamibarotene	Lotus Pharmaceutical	Retinoid acid receptor agonist	NME (ex. USA Only)	-
	TK	-	MolMed/Oxford BioMedica***	Hematopoietic cell	NME	-
Phase II^	Revlimid	lenalidomide	Celgene	Immunomodulator	NME	3
	Nexavar	sorafenib tosylate	Bayer/Onyx Pharmaceuticals/Zydus Cadila	Multi-kinase inhibitor	NME	9
	Jakafi/INCB18424	ruxolitinib phosphate	Novartis/Incyte	Janus kinase-1/2 (JAK-1/2) inhibitor	NME + Orphan Drug	8
	Votrient	pazopanib hydrochloride	GlaxoSmithKline	Multi-kinase inhibitor	NME	2
	Zolinza	vorinostat	Merck & Co	Histone deacetylase (HDAC) inhibitor	NME	1
	Mozobil	plerixafor	Sanofi	CXCR4 antagonist	NME + Orphan Drug	1
	LBH589	panobinostat	Novartis	Histone deacetylase (HDAC) inhibitor	NME	-
	GSK1120212	trametinib	GlaxoSmithKline/Japan Tobacco	MEK inhibitor	NME	-
	ABT-869	linifanib	Abbott Laboratories	Multi-kinase inhibitor	NME	-
	PLX3397	-	Daiichi Sankyo	FMS, c-kit & Flt-3 kinase inhibitor	NME	-
* WW ex N. America, ** N. America, *** Royalties					**Total available market sales ($m) (all indications)**	5
^Top 10 phase II drugs according to forecasted 2016 world wide sales (all indications)						

Try, try again

That failure has not discouraged drugmakers from trying, and analysts have even somewhat optimistically pencilling in a forecast in the indication for Novartis' PKC412 – roughly half of the $62m in total sales projected in 2016.

That candidate is currently in a 714-patient trial in combination with cytarabine and daunorubicin, with a primary endpoint of overall survival, with readout likely mid-2013. Notably, the first-line trial is in patients younger than 65 – not surprising given the chemotherapy combination – and thus a large proportion of patients must look elsewhere for hope.

That hope could come from Cyclacel and Daiichi Sankyo's CYC682, being studied first-line as a monotherapy and in combination with decitabine against decitabine alone in 470 patients older than 70, with overall survival a primary endpoint. That trial could report toward the end of 2013.

CYC682 is a pyrimidine analogue, similar to Clavis Pharma's most advanced candidate, Elacyt/CP-4055. The Norwegian company is targeting full enrolment of 380 in the Clavela trial later this year with topline results in the first quarter of 2013. Elacyt is being trialled against several treatment regimens in late-stage adult patients who have not responded to any previous medications or treatments, with overall survival the endpoint. Notwithstanding the 'investigator's choice' trail design with such a sick patient population, it might not take much of an improvement to achieve statistical superiority.

Sunesis and Dainippon Sumitoma's vosaroxin is due to read out from a phase III trial next year on the drug in combination with cytarabine in patients who are on their first relapse. The study in 500 patients will measure overall survival.

Established players

Established targeted therapies such as Revlimid, Nexavar, Votrient and Zolinza are prominent in phase II. Given the unmet need and the relatively low bar for approval, particularly in the elderly population, it is not too surprising to see the big and specialty pharma companies taking a shot on goal with their established targeted therapies. Incyte is also trialling its newly approved JAK inhibitor Jakafi.

Jakafi, the first JAK inhibitor approved, is among one of the two more novel drug classes represented in phase II. Another is GlaxoSmithKline's MEK inhibitor GSK1120212, currently in a safety, pharmacodynamic and pharmacokinetic trial in 120 leukaemia patients that could report soon.

The age and frailty of the AML population are proving to be a big barrier to optimal treatment in this category, a situation that cries out for treatments without the systemic toxicities of chemotherapy. Past failures might not necessarily lend much hope, but the size of the pipeline suggests that a breakthrough could come soon.