Paediatric Strategy Forum for Medicinal Product Development for Acute Myeloid Leukaemia in Children and Adolescents

ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration

11-12 April 2019

Summary

Context: The fourth multi-stakeholder Paediatric Strategy Forum, organised by ACCELERATE in collaboration with the European Medicines Agency (EMA) with participation of the Food and Drug Administration (FDA) was held at Erasmus University, Rotterdam and focused on acute myeloid leukaemia (AML) in children and adolescents. Paediatric Strategy Forums are multi-stakeholder (clinicians, academics, patient advocates, pharmaceutical companies and regulators) scientific meetings on specific topics regarding paediatric oncology. The Forums aim to share information and advance learning, which may inform subsequent strategic and regulatory decisions on the development of medicines for children with cancer. The goal of this meeting was to facilitate development of innovative medicines for the treatment of children and adolescents with AML, and ultimately, by extension, introduce these medicines into the standard-of-care for children.

The 5-year overall survival (OS) for paediatric AML currently is approximately 75%; however, the standard of care for frontline therapy for many decades has been daunorubicin and cytarabine. Furthermore, cardiotoxicity, due to anthracyclines, is an important long-term sequelae in a substantial proportion of survivors. AML is more frequent under the age of 3 years and its incidence initially declines and subsequently increases throughout young adulthood and is most frequent in the elderly. The occurrence of specific genetic alterations differs in AML in children compared to adults and the elderly. *NPM1, FLT3, IDH1, IDH2, RUNX1, DNMT3A* and *CEBPA* single-gene mutations are rare in children and their incidence gradually increases with age; however RAS pathway mutations are more frequent in children. In contrast some fusions such as those involving *KMT2A* (previously *MLL*) and Core Binding Factor (CBF) AML are commoner in children. The majority of children with AML, approximately 900 patients per year, in Europe, North America, Japan, Australia and New Zealand are enrolled on international cooperative group clinical trials.

Although there are many novel medicinal products being evaluated in adults with AML (8 authorisations in the last year), there are two main factors that make clinical development of adult AML drugs in children problematic: - i) children and adults have vastly differing profiles of genetic abnormalities and therefore targeted agents are often not applicable across all ages; ii) children and adults, especially the elderly, have differing toxicity profiles in response to new drugs. There is clearly a need for a different drug development process. The challenge is how to make the best choices of innovative medicines for children with AML, how to prioritise their inclusion in clinical trials and ultimately introduce these medicines into clinical practice. As the majority of patients are treated on international cooperative group trials, how to prioritise drug development of novel agents within the global regulatory framework and cooperative group initiatives is a further issue. At the Paediatric Strategy Forum there were international experts in paediatric AML and drug development; representatives from eighteen pharmaceutical companies and the Leukaemia Lymphoma Society; patient advocates from KickCancer and Unite2Cure and regulators from the EMA (including Paediatric Committee [PDCO]) and the US FDA. A comprehensive overview of the epidemiology, biology, diagnostics and therapeutic needs of paediatric patients with AML was

presented as well as the pharmacological and clinical information on twenty nine medicines being developed for the treatment of AML.

Current therapy of AML in Children and Adolescents at presentation: In newly-diagnosed paediatric patients with standard-risk disease, frontline therapy comprises 4 or 5 courses of intensive, cytarabine/anthracycline based chemotherapy. There is heterogeneity in the chemotherapy backbones between groups, with different types of anthracycline, different doses of anthracycline or cytarabine, and sometimes the addition of etoposide. Risk stratification has become more comprehensive in recent years and is based on cytogenetic and molecular characteristics, as well as measureable/minimal residual disease (MRD) in most collaborative group trials. Allogenic haematopoietic stem cell transplantation in first remission is standard of care in high-risk patients and improves survival. With this approach there are similar outcomes in the cooperative groups. Although the activity of gemtuzumab ozogamicin has been demonstrated in subgroups of AML (for example CD33 genotypes), it has not received regulatory approval for children. New or planned trials are addressing the role of CPX 351 (liposomal cytarabine and daunorubin; 'Vyxeos'), the optimal scheduling of gemtuzumab ozogamicin, FLT3 inhibitors and azacytidine (the latter in molecular relapse). In the future it is important to identify the subgroups of patients with AML who benefit the most from gemtuzumab ozogamicin. Due to differences in biology and more favourable outcomes, there are distinct therapeutic approaches and trials for AML associated with Down Syndrome and acute promyeloctyic leukaemia. Arrangements for the laboratory diagnosis and assessment of AML (in terms of definitions, risk group stratification and response assessment) are very similar across the cooperative groups allowing meaningful comparison of results.

Current therapy of AML in children and adolescents at relapse: 25-30% of children with AML relapse and 5% have disease refractory to initial induction therapy. On average, each year there are in Europe, North America, Australia, New Zealand and Japan in total 250 patients under the age of 19 years with relapsed/progressive disease but less than 20% of these patients are treated on a trial. Only 70% of relapsed patients achieve a complete remission and 5-yr OS is 30-40%. There are a variety of chemotherapy regimens utilised at relapse with FLA(G) (fludarabine and high dose cytarabine +/- granulocyte colony stimulating factor [GCSF]) and an anthracycline (frequently a liposomal format, which is currently not available in several countries) being the most commonly used, and the role of gemtuzumab ozogamicin is being evaluated. Allogeneic haematopoietic stem cell rescue is offered to all patients. CPX-351 may be attractive as a "backbone" chemotherapy in relapse, in view of the relatively high cumulative anthracycline dose most patients will have received during front-line therapy.

Therapeutic targets for AML in Children and Adolescents: *Paediatric and Adult Cell lineage target*:
Gemtuzumab ozogamicin targeting CD33 improves event free survival in a subgroup of patients. CD123 is differentially overexpressed in 93% of AML patients and is being targeted in adults via monoclonal antibodies, antibody-drug conjugates (ADCs), protein drug conjugates, bispecific T cell engagers and chimeric antigen receptor T Cells (CARTs).
Tyrosine kinase inhibitors – *FLT3* mutations occur in 10% of paediatric AML and even rarer are IDH1/IDH2 mutations (1 and 2%). *KIT* exon 17 mutations confer a worse prognosis and inhibitors such as crenolanib and dasatinib are being studied. RAS pathway mutations are significantly more common in children compared to adults and MEK inhibitors are under investigation.
Additional pathways **-** Pevonedistat is a first in class NEDD8 activating enzyme inhibitor, targeting the ubiquitin proteasome system. Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death.
Immune modulation **-** Tim3 plays a critical role in modulating immune reactions as an immune checkpoint. It is not expressed in normal marrow but is highly expressed in leukaemia stem cells**.**

Specific Paediatric Targets **-** *CBFA2T3-GLIS2* is an exclusively paediatric cryptic fusion, is associated with CD56 expression and a dismal prognosis. Mesothelin is a cell surface glycoprotein expressed on mesothelial cells including the pleura, peritoneum but not expressed in normal bone marrow. Menin - KMT2A (MLL1) are important targets for AML and ALL and specific inhibitors of the menin - MLL1 interaction are available.

Paediatric Investigation Plans (PIPs): There are currently (April 2019) 14 PIPs agreed for medicines for a condition related to the treatment of AML: gemtuzumab ozogamicin, CPX351, pevonedistat, isatuximab, venetoclax, volasertib, decitabine, azacitidine, guadecitabine, midostaurin, quizartinib, gilteritinib, enasedinib and ivosedinib. None of these PIPs are completed and no final compliance check yet conducted.

New medicinal products: Eight classes of medicinal products were discussed at the Forum: FLT3 inhibitors; IDH 1&2 inhibitors; monoclonal antibodies, BITEs and ADCs; checkpoint inhibitors, cell signalling & HDAC inhibitors and cytotoxics.

Class of medicinal product	Product	Target	Company
FLT3 Inhibitors	Midostaurin	FLT3	Novartis Pharmaceutical Industry AG
	Gilterinib	FLT3	Astellas
IDH 1&2 Inhibitors	FT-2102	IDH1	FORMA Therapeutics
	Ivosidenib	IDH1	Agios
	Enasedinib	IDH2	Celgene
Monoclonal antibodies, T cell engager and ADC	Flotetuzumab - Bispecific CD123-CD3 DART	CD123	Les Laboratoires Servier
	XmAb®14045 (SQZ622) (Bi-specific CD123-CD3) (intermittent dosing)	CD123	Novartis Pharmaceutical Industry AG
	SAR440324 CD3-CD123 T cell engager with weekly dosing	CD123	Sanofi
	Gemtuzumab ozogamicin (ADC)	CD33	Pfizer
	AMG 330 & AMG 673 (BITE CD33)	CD33	Amgen
	AMG 427 (BITE FLT3)	FLT3	Amgen
	Anetumab ravtansine (ADC)	Mesothelin	Bayer
	Cusatuzumab (monoclonal antibody)	CD70	Janssen
	Isatuximab (monoclonal antibody)	CD38	Sanofi
Checkpoint inhibitors	MBG453	Tim3	Novartis Pharmaceutical Industry AG
	Nivolumab, ipilimumab with azacitidine	PDL-1	BMS
Cell Signalling & HDAC Inhibitors and combinations	Venetoclax	BCL2	AbbVie jointly with Roche-Genentech
	Idasanutlin	MDM2	Roche-Genentech
	Siremadlin (HDM201) & MIK665/S64315	MDM2 and MCL-1	Novartis Pharmaceutical Industry AG
	BMS-986158	BET	BMS
	AMG 176 and AMG 397	MCL1	Amgen
	Alisertib	Aurora A kinase	Takeda Ltd
	Pevonedistat	NEDD8-activating enzyme	Takeda Ltd
	Pracinostat	HDAC	Helsinn HealthCare
Cytotoxic	Vyxeos (CPX-351)	Liposomal cytarabine and daunorubin	Jazz Pharmaceuticals

Table –Medicinal for AML discussed at the Paediatric Strategy Forum

Discussion and conclusions

Evaluation of novel medicinal products: Frequently there has been an interval of many years between a potentially valuable drug being evaluated in adults and then in children. Efforts should be made to accelerate the evaluation of these products in children, and prioritisation of these novel

agents within the global regulatory framework and cooperative group initiatives is critical. Whilst many novel drugs for AML are developed in older adults as monotherapy due to co-morbidities, there is a need to limit this approach in children who are more likely to tolerate, and benefit from, combinations with chemotherapy. Consensus approaches between clinical trial cooperatives and biopharmaceutical companies are particularly valuable to achieve these goals.

Frontline protocols: Although there are many approaches for children at presentation, it is not considered essential for progress or for conducting clinical trials that there is only one standardised frontline chemotherapy regimen. As a similar response to different frontline regimens has been observed: multiple cassettes can be included. However, it is critical that biological data is obtained from all patients and the same definitions for treatment response are used internationally.

Relapse protocols: A single chemotherapy backbone to which novel agents can be added and/or new treatment regimens can be compared would improve efficiency compared to the current diversity of approaches. Close collaboration between international clinical trial cooperative groups and the biopharmaceutical industry is essential, as is increasing the number of patients enrolled into relapse trials.

Master Protocols: Master protocols with a common screening platform to identify all trials for which a patient is eligible and an evaluation of more than one or two treatments within the same overall trial structure have an important role in the relapsed AML population. The trials would be industry supported, academically sponsored with compounds from different pharmaceutical companies and different mechanisms of action, using an adaptive design and conducted with “intent to file” i.e. collecting data that can be reliably utilised for regulatory submissions. The trials would be a collaborative effort between North America and Europe, to enrol the necessary number of patients in a rare setting. Hitherto opening academic trials on both sides of the Atlantic has been challenging. These protocols could be part of a regulatory package in Europe (i.e. included in a PIP) and fulfil FDA regulatory requirements in response to PREA (including planned amendments in 2020) and/or BPCA. Data generated by a master protocol could be part of *early* development (dose finding and signal seeking) and included in PIPs for the individual drugs. As PIPs require, in addition, studies generating pivotal evidence, a 'placeholder' study, of a ‘pivotal trial’ with all the relevant details need to be part of each of the individual PIPs, iPSPs, PPSRs - it would be important to uniformly define success criteria allowing the product to move forward (this will possibly be product specific). Companies should plan to submit their individual PIPs at the same time to the EMA for PDCO assessment and engage in early interactions (e.g. through request of CHMP scientific advice and/or PDCO pre-submission meetings) as well as early discussions with FDA and consider requesting a Common Commentary from EMA and FDA.

The Leukaemia & Lymphoma Society Pediatric Acute Leukemia (PedAL) initiative fulfils the need for a Master Protocol as it aims to collect all data on all patients, with central screening to permit efficiency in target identification and treatment recommendations. Its flexibility to engage the biopharmaceutical industry early and the intent to meet regulatory objectives provides a strong potential to standardise and unite global efforts in paediatric AML drug development.

MRD as an Endpoint and definitions of molecular remission and relapse: MRD is currently used for risk stratification and/or primary or secondary endpoint in paediatric clinical phase III trials, is included in regulatory submissions and maybe has the potential to become a surrogate marker of long-term outcome in AML. There is a biopharmaceutical company alliance evaluating MRD as a surrogate endpoint and there are many academic initiatives in this area. Similarly, there is variability in the definition of molecular remission and relapse. Techniques are available and further under development/evaluation in the study groups and consensus is lacking. Harmonisation, cross-validation of technology platforms, data-sharing, openness of standards and communication with FDA & EMA are essential to establish MRD as a surrogate marker of long-term outcome.

PIPs: Substantial concerns were raised by the clinicians and pharmaceutical companies present about the number of agreed PIPs (14), in view of the small number of eligible patients. The EMA

highlighted that a PIP and its obligations can be re-assessed at any time based on early results of a clinical study. If a study is for example showing lack of activity, a PIP can be modified accordingly. Similarly, if an early clinical trial shows promising results, the need for the agreed Phase III trial can be reconsidered.

Discussions among clinicians, cooperative groups and pharmaceutical companies should take place before PIPs are proposed to decide which compounds are most likely to be relevant for evaluation in the paediatric population with AML. Relevant scientific arguments from these discussions should be incorporated into the clinical study design and relevant regulatory applications. An academic-industry consensus would be of great benefit to regulators. Where a medicinal product is being developed in adult AML but thought less relevant for children, an upfront product specific waiver could be submitted. This waiver, would be supported by clinical trial cooperative groups based on scientific evidence or lack of therapeutic benefit, over existing authorised products (for children), or safety grounds. At the same time it was considered important to see the high number of agreed PIPs in context of the known high failure rate of novel compounds in early development. Rather than agreeing to waive products prematurely, it was highlighted to use deferrals to maintain feasible product development. However, this requires consolidated efforts by academia and industry, to agree to defer paediatric development of those products which are considered to be of high interest, but not highest priority based on current scientific knowledge.

FLT3 inhibitors: Approximately 90 paediatric patients per year present with *FLT3* mutations in North America, Europe, Australia and Japan. At the time of the Forum there were 2 FLT3 inhibitors with FDA approval in adults, 3 agreed PIPs for FLT3 inhibitors with 3 front-line and 2 relapse studies. It is highly unlikely that these trials could be completed in view of the numbers of available patients. It was proposed to organise a meeting, with the relevant biopharmaceutical companies and academics, to discuss the studies with FLT3 inhibitors and develop a consensus to propose to the regulatory agencies.

Rare mutations: *IDH1* mutations occur in 1% of children with AML i.e. approximately 10 patients per year in trials in North America, Europe, Australia, New Zealand and Japan, however the incidence is higher in adolescence. The incidence of IDH2 mutations is similar - 2%. It was concluded that the future approach for inhibitors of mutations which were very rare in children, but more frequent in adolescence is to include adolescents in adult trials and to consider discussing the possibility to extrapolate efficacy to younger children from adolescent data. The inclusion of “real world” data is a further approach**.**

CD 123 is a high priority target and it was proposed that CD 123 should be a proof of concept of how to accelerate the paediatric evaluation of products with greatest probability of being beneficial in view of their mechanism of action. This would comprise a consensus between the relevant biopharmaceutical companies and academics about prioritisation (particularly within the same class of agent, but also between agents with different mechanisms of action) and then discussion with regulatory agencies. In the relapsed population ADCs, which are administered with chemotherapy, have the advantage of not being reliant on a competent immune environment.

Conclusion: There is a major need to accelerate the introduction of innovative medicines into the therapy of children and adolescents with AML. A number of competing agents of the same class in a rare population presents a challenge and therefore prioritisation is required. The Leukaemia & Lymphoma Society PedAL Master Trial with compounds from different pharmaceutical companies should fulfil many of the requirements for an industry supported, academic sponsored study which could collect relevant data to identify the products to be further developed in paediatric AML. It was agreed to convene meetings to consider the development of FLT3 inhibitors and medicinal products targeting CD123 (both as proof of concepts), a consensus of MRD as a surrogate marker for long term outcome, and definitions of molecular remission and relapse.