EUROPEAN HEMATOLOGY ASSOCIATION

Acute myeloid leukemia - Section 3

3+7 and beyond

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Take-home messages

- 3+7 is the standard of care for AML a is used as a chemotherapy backbone
- Many new therapies have recently emerged which target cell surface markers, mutated genes, deregulated pathways or immune response
- Variety and complementarity of their mechanisms of action make it possible to action several cellular pathways (eg. apoptosis or signaling) or cell populations (eg. LSCs or immune effectors) and to envisage the development of multi-agent combination regimens.
- They may challenge the current paradigm of AML therapy and open prospects for chemo-free therapies.

Introduction

'3+7' generally refers to the combination of an anthracycline (daunorubicin or idarubicin given over 3 days) to cytarabine (given at conventional doses of 100 to 200 mg/m²/day over 7 to 10 days) that is the mainstay of acute myeloid leukemia (AML) induction chemotherapy since the last 30 years. Improvements on the original combination regimen have been the goal of many clinical trials conducted by cooperative groups all over the world during this period. This research has been productive as an international consensus has been achieved.[1] On the other hand, limited progress has been made contrasting with those achieved in other hematologic malignancies such as lymphoma, myeloma or chronic leukemias during the same period of time. Up to now, most of the attempts to improve on 3+7 were based on dose intensification or the addition of new drugs. However, this paradigm may be challenged because: 1) new potentially active therapies with various and original mechanisms of action (MoA) have emerged, and 2) the acute promyelocytic leukemia (APL) model demonstrates that 'chemo-free' treatment approaches (combination of retinoic acid and arsenic) are more effective than conventional treatments. Thus, we may wonder if time has come to change our paradigm and get rid of 3+7.

The strengths and weaknesses of 3+7

3+7 can induce complete remission (CR) in 60-80% of younger adults and in 40-60% of older adults that are fit for intensive therapy.[2] Blast clearance is generally obtained in few days and approximately two-third of the patients have empty marrow by day 15. This may be beneficial in AML and especially in forms with hyperleucocytosis associated with life-threatening complications. 3+7 may therefore represent an optimal debulking strategy. However, relapse that occur in the majority of patients remains an issue as well as toxicity which limits the applicability of 3+7 in elderly frail patients. Attempts to improve on 3+7 have included: 1) intensification of the anthracycline dose; 2) the use of high or intermediate doses of cytarabine (HIDAC); 3) double induction strategies;and 4) the addition of a third drug to the 3+7 'backbone'. Although still a matter of debate, the findings of several large multicenter randomized trials indicate that optimal daunorubicin doses range between 60 to 90 mg/m² while the benefit of replacing daunorubicin by idarubicin or conventional doses of cytarabine by HIDAC is not yet established.[1] Several attempts have been made to add a third drug to 3+7. The anti-CD33 antibody-drug conjugate (ADC) Gemtuzumab ozogamycin (GO) showed conflicting results, but a meta-analysis demonstrated a survival improvement in patients with non-unfavorable cytogenetics.[3] Cytotoxic agents such as clofarabine,[4,5] cladribine,[6] or lomustine,[7] gave conflicting or not-yet-confirmed results. The lack of consistent effects across trials reflects the weak activity of these drugs. Another issue is toxicity that balances the benefits of attempts to increase chemotherapy dose-intensity or to add a third drug. Finally, 3+7 is a 'one-size-fits-all' approach that disregards the molecular and genetic heterogeneity of AML.[8] This underlines the need for new agents with new MoAs and greater therapeutic index.

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The addition of new drugs to reinforce 3+7

Many new drugs are currently in clinical development and are summarized in Table 1. This list is not meant to be exhaustive but rather to give a snapshot of the variety of therapeutic classes and MoAs. It also deliberately omits FLT3 inhibitors that are discussed in the previous chapter of this review (see Section 2 - Targeting mutated FLT3 in acute myeloid leukemia).

New cytotoxic drugs may be used instead of or be added to 3+7. CPX-351 is an encapsulation in nano-scale liposomes of cytarabine and daunorubicin and has shown superior CR and survival as compared to 3+7 in elderly patients with secondary

Table 1. New agents in clinical development.

Therapeutic class	Drug	Patients	Status
Cytotoxic agents			
Liposomal D+A	CPX 351	HR elderly AML frontline	Rando Phase 2
Topo-II inhibitor	Vosaroxin	R/R AML	Phase 3 R/R
Monoclonal antibodies			
AntiCD33 mAb	Iintuzumab	Misc.	Phase 3
AntiCD33 ADC	GO	frontline	Phase 3
	SGN-33A	R/R AML +frontline	Phase 3 combo
AntiCD33/CD3	AMG330	R/R AML	Phase 1 single agent
Anti-CD123 mAb	Talacotuzumab	R/R AML	Phase 2 combo
Anti-CD123 ADC	SGN-CD123A	R/R AML	Phase 1 single agent
Anti-CD3/CD123	MGD006	R/R AML	Phase 1 single agent
	JNJ-63709178	R/R AML	Phase 1 single agent
Apoptosis targeting agents			
BCL2-i	Venetoclax	R/R AML	Phase 2 combos
	S55746	R/R AML	Phase 1
MCL1-i	S64315	R/R AML	Phase 1
MDM2-i	Idasanutlin	R/R AML	Phase 3 combo
Kinase/Cell cycle-i			
PIM kinase-i	CLGH447	R/R AML	Phase 1 combo
MEK-i	Cobimetinib	R/R AML	Phase 1 combo
PI3K/RAS-i	Rigosertib	R/R AML	Phase 1
CDK-i	Palbociclib	R/R AML	Phase 1
Epigenetic drugs			
Oral azacitidine	CC486	Frontline	Phase 3 combo
Decitabine prodrug	SGI-110	Frontline elderly	Phase 3
Bromodomaine-i	OTX015	R/R AML	Phase 1
DOTL1-i	EPZ-5676	R/R MLL AML	Phase 1
Immunotherapy			
ICB			
Anti-CTLA4	Ipilimumab	R/R AML	Phase 1-2
Anti-PD1	Nivolumab	R/R + frontline AML	Phase 1-2 combo
Anti-KIR	IPH2101	R/R AML	Phase 1
	Lirilumab	frontline elderly AML	Phase 2-3
Anti-NKG2A	Monalizumab	Maintenance post allo	Phase 1
CAR-T cells			
Anti-CD33	CART33	R/R AML	Phase 1
Anti-CD123	CART123	R/R AML	Phase 1
Anti-CD133	CART133	R/R AML	Phase 1
Others			
Nuclear export-i	selinexor	Frontline AML	Phase 3
Hedgehog-i	Sonidegib	Frontline R/R AML	Phase 1 combo
	PF-04449913	Frontline AML	Phase 2

AML.[9] Vosaroxin is a quinolone derivative shown to improve survival in elderly patients with refractory/relapsed AML when given in combination with IDAC[10] and is currently being evaluated in addition to 3+7.

Cell surface antigens such as CD33 and CD123 represent attractive targets for monoclonal antibodies (mAb), ADCs, bispecific antibodies or chimeric antigen receptor T-cells (CART). The prior experience with GO has validated the therapeutic relevance of CD33.[3] CD123 is expressed by the Leukemic Stem Cell (LSC) compartment. CD123 directed therapeutic strategies have therefore the potential to target LCS which may persist after remission and represent a relapse reservoir.

Small molecules can target products of mutated genes such as FLT3 (see Section 2) or IDH1 and 2, of overexpressed proteins involved in a variety of pathways including signaling (RAS, KIT, PIM), apoptosis (BCL2 family members, TP53) or of epigenetic regulators (DNA methytransferases, bromodomaines or DOT1L). Some of them have shown encouraging clinical activity in phase 1 and 2 studies and are currently in phase 3, like venetoclax, a BCL2 inhibitor,[11] idasanutlin a MDM2 inhibitor[12] or Selinexor (a nuclear transport protein exportin (XPO1) inhibitor). Trials of their combination with 3+7 frontline are underway (NCT02545283, NCT02403310).

Finally, immunotherapeutic approaches are appealing in AML for which a body of evidence supports the rationale for a role of immune effectors (T-cells and NK-cells) in the control of the disease.[13,14] Anti-KIR[15] and anti-NKG2A mAbs may block inhibitory signals and therefore promote anti-leukemic NK-cell cytoxicity. Immune checkpoint blockade using anti-PD1/PDL1 or anti-CTLA4 are currently being investigated in AML.(13) Preliminary congress reports suggest limited single agent clinical activity and combination studies are underway.

Classical clinical development paths involve the addition of new agents to a 3+7 backbone, and many of the above-mentioned drugs are currently tested accordingly. However, their wide variety of MoAs opens new perspectives, including the design of chemo-free therapies that follow an 'APL paradigm'. The molecular heterogeneity of AML predicts the failure of single-target approaches and future work should focus on the clinical evaluation of combinations, the rationale of which is already supported by many preclinical evidences. For instance, preclinical data suggest synergism between BCL2-inhibitors and MCL1-inhibitors or IDH1/2 inhibitors while ICP blockade might reinforce T-cell activation following treatment with bispecific anti-CD3 antibodies. In this perspective, new agents may be viewed as part of therapeutic platforms targeting actionable biological functions such as apoptosis (BCL2 family members inhibitors, MDM2 inhibitors), immune response (ICP blockade, anti-KIR) and signaling (multi-kinase-inhibitors, anti-FLT3, anti-MEK, etc.) or leukemic sub-populations like LCS (anti-CD123, Hhg inhibitors).

In this perspective, the future of AML therapy -beyond 3+7- might be the development of chemo-free strategies built on the right combination of the various therapeutic platforms, like the blocks of a building game, adapted to the various patient population and leukemia subgroups. Moving fast from utopia to reality, we have already embarked in these new approaches and several multi-agent combinations trials are underway.

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