

The Case for Intensive Chemotherapy in Fit Newly Diagnosed AML

A Debate Presentation

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AML Is a Medical Emergency — Intensive Chemo Answers the Urgency

- **10–20% of AML patients present with hyperleukocytosis (WBC >100K), and 21% have DIC at diagnosis [1-3]**
- DIC-positive patients have 30-day mortality of **42.5%** vs 8% without DIC [2]
- **23% develop tumor lysis syndrome** during induction [4]
- Leukostasis mortality: **20–40% die within the first week** if untreated [3]
- These emergencies demand rapid, definitive cytoreduction — intensive chemotherapy delivers this within days
- HMA/VEN requires a **3–5 day venetoclax ramp-up** and carries its own TLS risk (OR 7.52 for venetoclax-based therapy) [4]
- **Key Point:** AML frequently presents as a hematologic emergency. Intensive chemotherapy provides the fastest, most definitive cytoreduction.

Intensive Chemo — The Only Approach With Category 1, Level 1 Evidence in Fit Patients

- NCCN Guidelines list **7+3 as category 1, preferred** for favorable/intermediate-risk AML [5]
- **7+3 + midostaurin: Category 1** for FLT3-mutated AML (RATIFY trial) [5-6]
- **7+3 + quizartinib: Category 1** for FLT3-ITD AML (QUANTUM-First) [5-6]
- **CPX-351: Category 1, preferred** for secondary AML age ≥ 60 [5]
- HMA/VEN is listed as "Other Recommended" — not preferred — for intensive-induction-eligible patients [5]
- **No randomized phase 3 trial has demonstrated superiority of HMA/VEN over intensive chemotherapy in fit patients**

MRD — Intensive Chemotherapy Achieves Deeper Responses

- Intensive chemotherapy achieves **MRD-negative remission** in ~**50–60%** of patients [7]
- Venetoclax + intensive chemo pushes this to **82–96% MRD-negative CRc** in phase 2 studies [7]
- In contrast, **VIALE-A (HMA/VEN in unfit patients)**: only **23.4% MRD negativity** by flow cytometry [8]
- Ven + 7+3 (phase 1b): **86.2% MRD-negative** among responders with median recovery <30 days [9]
- CLIA-VEN: **93.8% MRD-negative CRc** vs 40.9% with 7+3 alone [10]
- **Key Point:** The intensive chemotherapy backbone — especially when combined with venetoclax — achieves the deepest MRD-negative responses, which is the strongest predictor of long-term survival.

The Quality of CR Matters — CR vs CRi

- Intensive chemotherapy achieves **true CR** (full count recovery) at higher rates
- HMA/VEN frequently achieves **CRi (CR with incomplete hematologic recovery)** — counts remain suppressed
- VIALE-A: CRc rate 66%, but **CR rate only 36.7%** — nearly half of responses were CRi [8]
- CRi is associated with **inferior OS** compared to CR, reflecting incomplete marrow recovery
- Patients in CRi on HMA/VEN require ongoing dose modifications, cycle delays, and G-CSF support [5][11]
- Intensive chemo patients who achieve CR have **fully functional hematopoiesis**, enabling timely consolidation and transplant

The Cytopenias Problem — HMA/VEN Is Not "Low Toxicity"

- HMA/VEN causes **prolonged and profound cytopenias** that are well-documented [11-12]
- Median time to ANC recovery after cycle 1 of HMA/VEN: **37–39 days** [13]
- Cycle delays of **up to 14 days (or longer)** are routinely recommended to allow count recovery [5]
- Venetoclax duration must be progressively shortened (from 28 → 21 → 14 → 7 → 5 days) in subsequent cycles to manage myelosuppression [5][14]
- Real-world data show **high rates of therapy discontinuation** due to myelosuppression [14]
- Intensive chemo: cytopenias are expected and time-limited — marrow recovery is typically assessed by **day 21–28**, with consolidation starting on schedule [5]
- **Key Point:** The narrative that HMA/VEN is "gentler" is misleading. Prolonged cytopenias, cycle delays, and dose reductions are the norm, not the exception.

Favorable-Risk AML — Intensive Chemo Is the Clear Winner

- **Core binding factor (CBF) AML** [t(8;21), inv(16)] — the best-prognosis AML subtype
- NCCN recommends **7+3 + gemtuzumab ozogamicin as preferred** for CBF-AML [5]
- High-dose cytarabine consolidation is the standard, with **3–4 cycles achieving 5-year OS >60%** [5]
- HMA/VEN performs **poorly in CBF-AML**: VEN-DEC showed **inferior CRc in RUNX1::RUNX1T1** (44% vs 88% with IC) [15]
- Meta-analysis: pooled ORR with HMA/VEN in RUNX1::RUNX1T1 AML was **significantly lower** (RR 0.44) [16]
- CBF-AML represents a substantial proportion (~15–20%) of AML patients
- **Key Point:** For the significant subset of favorable-risk AML, intensive chemotherapy is unequivocally superior. HMA/VEN should not be used for these patients.

Targeted Agents Synergize With Intensive Chemo — A Proven Platform

- **Midostaurin + 7+3 (RATIFY):** 4-year OS 51% vs 44%, HR 0.78 (p=0.009) [6][17]
- **Quizartinib + 7+3 (QUANTUM-First):** OS HR 0.78 (p=0.03), FDA-approved [6][18]
- **Gemtuzumab ozogamicin + 7+3:** Improved survival in favorable/intermediate-risk CD33+ AML [5]
- **CPX-351:** Median OS 9.56 vs 5.95 months vs 7+3 in secondary AML (HR 0.69, p=0.003); post-transplant 3-year OS **58% vs 29%** [17][19]
- These are **category 1 combinations with phase 3 randomized data**
- **Key Point:** No equivalent randomized data exist for adding targeted agents to HMA/VEN as a frontline platform in fit patients

Intensive Chemo + Venetoclax — The Best of Both Worlds

- Venetoclax can be **added to intensive chemotherapy**, not just to HMA
- FLAG-IDA + VEN, CLIA + VEN now listed in NCCN for poor-risk AML [5]
- CAVEAT trial (5+2 + VEN): 72% CRc in older patients, **97% in de novo AML** [20]
- Ven + 7+3 (phase 1b): **85.3% CRc, 86.2% MRD-negative, 0% induction deaths** [9]
- CLIA-VEN: 90% CRc vs 54.8% with 7+3 alone, improved OS on propensity-weighted analysis [10]
- This approach preserves the intensive backbone while adding BCL-2 inhibition
- **Key Point:** The argument is not "chemo vs venetoclax" — the best outcomes may come from combining both, which requires an intensive backbone.

Alternate Delivery Platforms Make Intensive Chemo More Practical

- **CPX-351 (Vyxeos):** Liposomal formulation delivers synergistic 5:1 cytarabine:daunorubicin ratio directly to leukemia cells [19]
 - Days 1, 3, 5 dosing schedule — simpler than traditional 7+3
 - Lower early mortality (5.9% vs 10.6% at day 30) [19]
 - Particularly benefits patients with MDS-related mutations (SRSF2, SF3B1, ASXL1, etc.) [5][21]
- **Outpatient (Hi)DAC consolidation (Days 1, 2, 3):** Intermediate-dose cytarabine on a 3-day schedule enables outpatient delivery for consolidation
- **Key Point:** These innovations address traditional concerns about prolonged hospitalization with intensive chemo

Bridging to Transplant — Intensive Chemo Gets More Patients There

- Allogeneic HCT remains the most effective post-remission therapy for intermediate/adverse-risk AML
- Intensive chemo + VEN: **79% of responding patients bridged to HSCT** vs 57% with IC alone [7]
- CPX-351: Post-transplant 3-year OS **58% vs 29%** compared to 7+3 [17]
- In FLT3-ITD AML, transplant after IC: OS **52.6 vs 22.7 months** (IC) and **38.6 vs 14.0 months** (LIT) [22]
- HMA/VEN: While transplant is feasible, the indefinite treatment model with ongoing cycle delays can make transplant timing **more unpredictable**
- **Key Point:** Intensive chemo provides a **defined induction → consolidation → transplant pathway**

Weaknesses of HMA/VEN — What the Opposition Won't Tell You

- **No cure without transplant:** HMA/VEN is a continuous therapy with no defined endpoint — patients relapse when treatment stops [11-12]
- **Prolonged myelosuppression:** Median ANC recovery 37–39 days; progressive dose reductions needed [5][13]
- **Infectious complications:** VEN-HMA is myelosuppressive with higher neutropenic fever risk than HMA alone; febrile neutropenia 36–55% [20][23]
- **Drug interactions:** CYP3A4 interactions with azole antifungals require VEN dose reductions (to 100mg with posaconazole), complicating management [13]
- **Prior HMA exposure limits benefit:** Patients with prior HMA exposure (post-MDS) derive less benefit from HMA-based regimens [5]
- **Poor in CBF-AML:** Significantly inferior in RUNX1::RUNX1T1 (44% vs 88% CRc) [15]
- **Real-world discontinuation rates are high** [14]

The Sequencing Argument — IC First Preserves Options

- **Chemo → HMA/VEN:** Patients who relapse after IC can be effectively salvaged with VEN-based regimens [12]
- **HMA/VEN → Chemo:** Outcomes after HMA/VEN failure are **dismal** [12]
 - Prior HMA exposure limits benefit from retreatment with HMA-based combinations [5]
 - Salvage intensive chemo after HMA/VEN failure has poor response rates
- **IC as induction preserves the full spectrum of salvage options**, including VEN-based therapy at relapse
- Starting with HMA/VEN in a fit patient burns a valuable option prematurely
- **Key Point:** Sequencing matters. Using the most effective therapy first (IC) preserves HMA/VEN as an effective salvage strategy.

Head-to-Head Data — Early Randomized Trials

Support IC

- **Lu et al. (NCT05177731):** VEN-DEC vs IC in young fit AML (age 18–59) [15]
 - CRc: 89% vs 79% (non-inferiority met), BUT:
 - **CBF-AML: 44% vs 88% CRc with IC** — dramatically inferior with VEN-DEC
 - All responders received **HiDAC consolidation** (i.e., needed intensive chemo anyway)
 - OS/PFS similar at short follow-up (12.1 months)
- **Meta-analysis (15 studies, 3,809 patients):** HMA/VEN vs IC [16]
 - CR: RR 1.05 (NS); CR/CRi: RR 1.09 (NS); 30-day mortality: RR 0.86 (NS)
 - OS favored HMA/VEN overall (HR 0.80), BUT driven by older/unfit patients and NPM1-mutated subgroup
 - **No OS benefit in favorable-risk genetics**
- These data do not support replacing IC with HMA/VEN in fit patients

Summary — Why Intensive Chemotherapy Remains the Standard

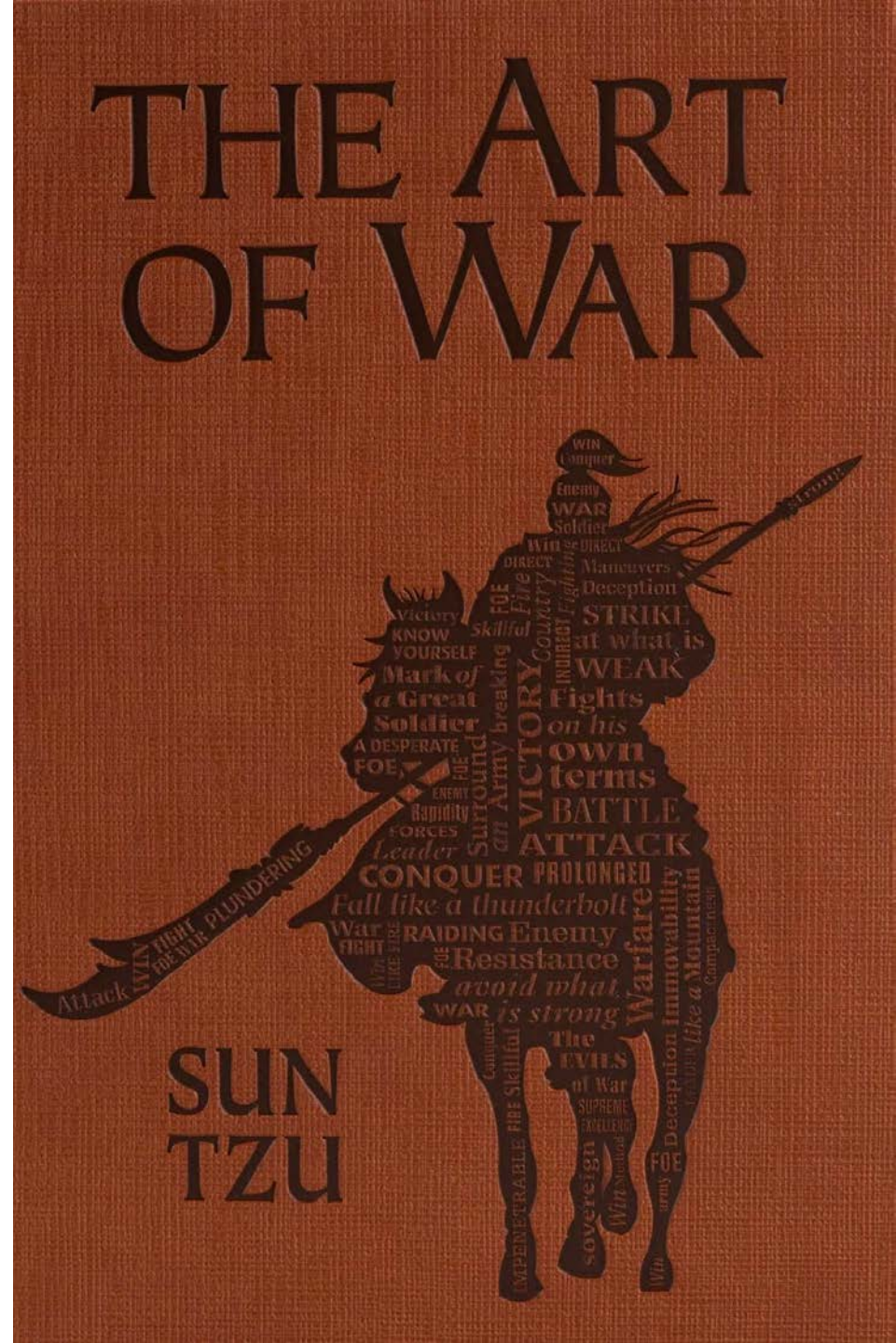
Argument	Intensive Chemotherapy	HMA/Venetoclax
Evidence level	Category 1, Phase 3 RCTs	Category 2A (in fit patients)
CR rate (true CR)	60–80%	36.7% (VIALE-A)
MRD negativity	50–60% (IC); 82–96% (IC+VEN)	23.4% (VIALE-A)
CBF-AML	Excellent (CRc 88%)	Poor (CRc 44%)
Targeted agent synergy	Midostaurin, quizartinib, GO, CPX-351 (all Cat 1)	Limited randomized data
Bridge to transplant	Defined pathway, high rates	Possible but unpredictable timing
Curative potential	Yes (with consolidation $\pm$ HCT)	Requires continuous therapy without HCT
Post-failure options	HMA/VEN available as salvage	Limited options after HMA/VEN failure

But,

from Sun Tzu (The Art of War): "He will win who knows when to fight and when not to fight." The wisdom is not in fighting every battle, but in knowing which battles to fight.

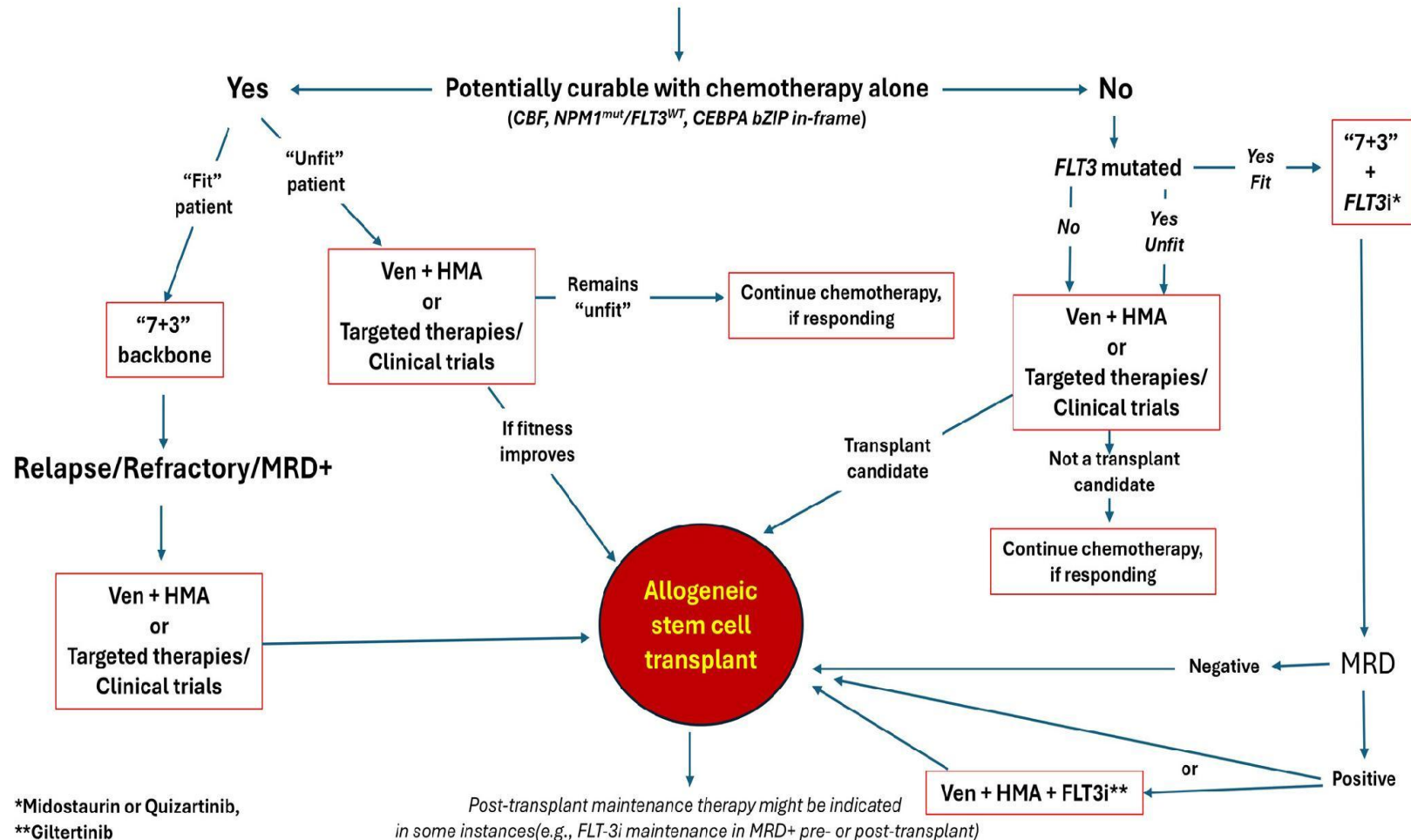
Image from:

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Since we are all friends ...

Acute myeloid leukemia treatment strategies in the era of venetoclax



The Tauro–Tefferi framework is not "chemo vs venetoclax" — it is biology-directed assignment of the right platform to the right patient, with allogeneic transplant as the shared curative endpoint.

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Hold the line with intensive 7+3-based therapy:

- **Genomically favorable, chemo-curable disease** — CBF-AML [t(8;21), inv(16)], NPM1-mutated/FLT3-wildtype, and CEBPA bZIP in-frame AML, where 7+3 remains the reference induction backbone and cure with chemotherapy $\pm$ transplant is achievable
- **Fit patients where deep MRD-negative remission and a defined path to consolidation/transplant are the goal**
- **Settings where targeted agents plug into the intensive backbone** — FLT3 inhibitors (midostaurin, quizartinib), gemtuzumab ozogamicin, CPX-351 for MDS-related disease

Relent gracefully to HMA–venetoclax (retreat where the odds favor a different weapon):

- **Patients unlikely to be cured by, or to tolerate, intensive chemotherapy** — older/unfit patients and much of ELN adverse-risk disease, where the PARADIGM signal (improved EFS, higher response, lower early mortality, better QoL, more patients reaching alloSCT) favors venetoclax-based lower-intensity therapy [1]
- **Contexts where 7+3 is known to underperform** — a graceful concession, not a defeat, and consistent with the commentary's honest reading of the data [1]

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