Acute leukemia

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Acute Myeloid Leukemia

High-Risk AML

Clinically and biologically distinct sizable (50%) group of patients with impact on treatment outcome (therapy-refractory, relapse within 1 yr and/or low survival rate)

- Clinical variables: therapy-related; arising out of an antecedent hematologic disturbance; in the elderly; WBC↑, LDH↑ at presentation, male gender; MRD after consolidation; PS; co-morbidity; refractory to induction; relapse after allo-HSCT or after recent consolidation.
- Biological variables:
  - Karyotype: complex (3 or more) abnormalities, monosomies of any chromosome (typically chromosome 5 and/or 7), inv(3), t(3;3), t(6;9), the rare t(9;22), 17p abnormalities, 11q23 abnormalities other than t(9;11)
  - Mutations: *FLT3/ITD*, mutant *TET2* or *IDH1/IDH2*, *MLL-PTD*, *DNMT3A* (especially in 'intermediate risk' normal-karyotype AML), c-kit (especially in 'favorable risk' t(8;21), inv(16) or t(16;16) AML).

Routine Evaluation of AML for Risk Stratification (Gary Schiller, UCLA)

Standard

- Morphology
- Flow cytometry/immunohistochemistry
- FISH for common abnormalities: t(8;21) *RUNX1-RUNX1T1*; inv(16) or t(16;16) *CBFB-MYH11*; t(15;17) *PML-RAR*α; t(9;11) *MLLT3-MLL*; inv(3) or t(3;3) *RPN1-EVI1*
- Karyotype
- Molecular studies for mutations in *FLT3*, *NPM-1*, *Kit*, *CEBPα*

Potentially useful

- Molecular studies for mutations in *DNMT3*, *TET2*, *MLL*, IDH1, and/or *IDH2*

Progress in the Therapy of High-Risk AML?

- No established or confirmed improvement in overall survival (OS) when adding different agents (eg. clofarabine, gemtuzumab, higher dose of chemotherapy). [DNR 90 vs. 45 mg/m^2 no benefit in high-risk AML].
- FLT3 tyrosine kinase inhibitors (TKI) midostaurin, lestaurtinib, quizartinib, and sorafenib: single-agent activity in the relapsed setting; quizartinib most promising for relapsed disease, but may select for mutations that confer resistance.
- Allo-HSCT at present only (post-consolidation) treatment that seems to work, especially for patients with intermediate-risk cytogenetics and patients with *FLT3/ITD* or adverse cytogenetics AML (retrospective studies), not for patients with advanced disease.

Core-Binding Factor (CBF) AML (1)

- AML with t(8;21) or inv(16) or t(16;16): good prognosis (90% CR, 50% cure with chemotherapy, especially high dose Ara-C in consolidation).
- Genetic heterogeneity of CBF AML: *RAS*, *KIT* , *FLT3* mutations.
- KIT or FLT3 TKI: already in trials in combination with conventional chemotherapy; use of TKIs as an adjunct to chemotherapy in CBF AML only recommended within clinical trials.
- Allo-HSCT not recommended to be generally offered as frontline treatment for CBF AML.
- Unclear whether patients with CBF AML and *KIT* or *FLT3* mutations benefit from allo-HSCT in CR1; to be investigated in clinical trials.

Core-Binding Factor (CBF) AML (2)

- No influence on current patient management → no routine *KIT* mutation screening at diagnosis of CBF AML. But: data on *KIT* and *FLT3* mutations needed within clinical trials, especially if TKI used.
- MRD in CBF AML recommended at baseline, after each treatment cycle and every 3 months during follow-up. Impending relapse: close monitoring and availability of a HLA-compatible donor. Not enough evidence for preemptive therapeutic interventions in CBF-AML based on MRD follow-up.
- Allo-HSCT as a salvage option for relapsing CBF AML (Robert Paschka, University Hospital of Ulm).

FLT3/ITD AML

- Adverse effect of *FLT3/ITD* on prognosis of AML, except in M3 AML/t(15;17); unclear effect on MDS/AML and on AML in patients older than 65.
- Impact of the length of *ITD* on clinical outcome: longer mutations are usually (but not always) associated with reduced remission rate and/or worse overall survival.
- Allelic ratio: ratio of *ITD*-mutated to wild type alleles
  - Higher allelic ratio predictive of worse outcomes, with loss of the wild-type allele being the worst
  - But limited sensitivity of *FLT3/ITD* assay:
    - PCR primers used to amplify the mutant allele also amplify the wild-type allele (increasing the number of PCR cycles will not increase the sensitivity)
    - Competitive advantage of the shorter wild-type allele; the longer the ITD, the greater the PCR bias; bias minimized by decreasing the number of PCR cycles, but this can decrease sensitivity when there is a low burden of leukemic cells in the sample.

FLT3/ITD ASSAY

- Allelic ratio: ratio of ITD-mutated to wild type alleles is influenced by:
  - the amount of malignant vs. nonmalignant cells
  - percentages of cells with 0, 1, or 2 mutated alleles
    - At diagnosis: polyclonal at presentation with, in most cases, dominant clone heterozygous for the mutation; subpopulations can lack the mutation; other can be biallelic; other be hemizygous for the mutant allele, by loss of the chromosome 13 containing the wild-type allele or through a smaller deletion of the wild-type
    - At relapse/progression: dominant clone emerges and the allelic ratio generally increases; in most cases: mutation originally detected at diagnosis also present at relapse. Occasionally, ITD undetectable at relapse (typically seen in cases with low allelic ratio (eg. 5%-15%) at diagnosis) → *FLT3/ITD* mutations have been regarded as unsuitable for use as a MRD marker.

FLT3 INHIBITORS

- Midostaurin, lestaurtinib, sorafenib, quizartinib, ponatinib, PLX3397.
- Quizartinib: so far, most potent, most selective and most tolerable FLT3 inhibitor at doses that completely inhibit FLT3 *in vivo*.
- Phase II trial: 191 relapsed/refractory *FLT3/ITD* AML patients, 2 cohorts treated with quizartinib as single-agent therapy (1st cohort: 92 older patients (median age 69 yr), relapsed/refractory to a single line of therapy; 2nd cohort: 99 younger patients (median age 55 yr) relapsed/refractory after 2 lines of therapy. CR (CR + Cri) 51%. Responses associated with rapid apoptosis of circulating blasts coupled with the induction of terminal differentiation of BM blasts over the course of a few weeks; no systemic toxicity. This allowed 47/136 patients (35%) of cohort 2 to undergo allo-HSCT with a significant number of long-term survivors from this very poor-risk group.
- Patients with response to quizartinib: often resistance, usually at D835 and less frequently at F691 → development of new TKI with activity against these new mutants.

ALLO-HSCT FOR *FLT3/ITD* AML

- No prospective studies regarding the place of allo-HSCT in *FLT3/ITD* AML.
- Most (retrospective) studies: *FLT3/ITD*+AML patients who undergo allo-HSCT in CR1 have a better outcome than those treated with conventional consolidation chemotherapy only, but still relapse at a higher rate than transplanted *FLT3/ITD*-AML patients. Thus: *FLT3/ITD AML* patient in CR1 should be offered a sib allo-HSCT as consolidation. Also, start MUD search, as soon as diagnosis of a *FLT3/ITD* AML; maybe: if no sib donor, decide on a MUD allo-HSCT, depending on *FLT3/ITD* allelic ratio and on concomitant NPM1 mutation (Mark Levis, Johns Hopkins University, Baltimore). No reliable data comparing myeloablative vs. reduced-intensity conditioning.
- Paradigm for future: add FLT3 inhibitors to induction chemotherapy of *FLT3/ITD* AML to increase the remission rate and to maintain CR, so the patient can be taken to allo-HSCT; after transplantation, the TKI could be used as maintenance therapy (cfr. TKI in the successful treatment of Ph+ ALL).

Allogeneic Hematopoietic Stem Cell Transplantation For Aml (Koen Van Besien)

Selection of Matched Unrelated Donor

- High resolution typing of HLA A, B, C, DR (1 mismatch (mm) reduces 1-yr OS by 10%)
- CMV-negative rather than CMV-positive for CMV- patients
- Male rather than female
- Younger rather than older
- Donor blood group
- KIR: different models are not entirely compatible with each other, refining necessary.
- HLA DPB1: only 25% match in 8/8 matched donor; some DPB1 mm are tolerated, others not (Zino et al. *Blood* 2004); by chance 50% permissive DPB1 mm; non-permissive DPB1 mm: ↑ transplant-related mortality, ↓OS (Crocchiolo et al. *Blood* 2009; Fleischhauer et al. *Lancet Oncology* 2012) → selection of donor with DPB1 match or permissive mm.

blood
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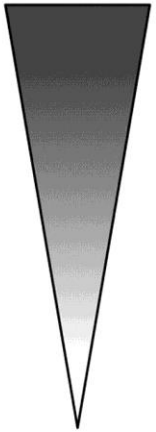
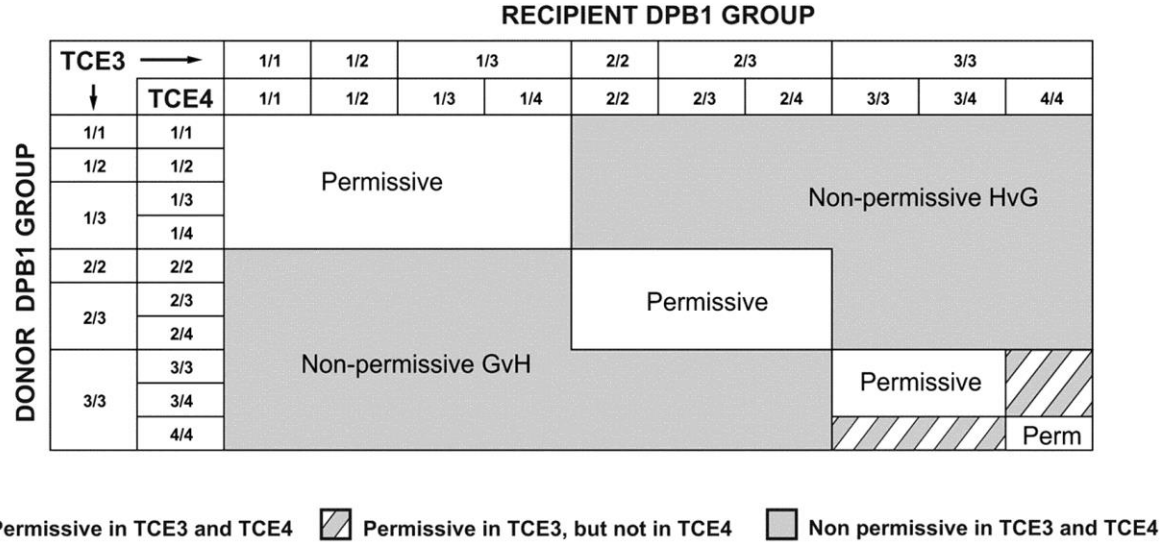
An algorithm for nonpermissive HLA-DPB1 disparities according to TCE3 or TCE4

A

DPB1* alleles	TCE3 group	TCE4 group	Immunogenicity
0901 1001 1701	1	1	
0301 1401 4501	2	2	
0201 0202 0203	3	3	
Others		4	

B



Crocchiolo R et al. Blood 2009;114:1437-1444

Chronic GvHD

- Beneficial against relapse in the short term, but detrimental on OS in the long term (F. Baron et al. *Leukemia* 2012; Weisdorf et al. *BBMT* 2012).
- GvHD at 2 yr post-HSCT (Bhatia et al. *Blood* 2007):
  - No → OS at 10 yr 92%
  - Yes → OS at 10 yr 73% (RR non-relapse-related mortality (GvHD, infections, cardiac): 3.4; RR relapse-related mortality: 1.8)
- With standard GvHD prophylaxis (calcineurin inhibitor + MTX), cumulative incidence at 2 yr of:
  - cGvHD: with BM 41%, with PBSC 53%
  - Extensive cGvHD: with BM 32%, with PBSC 48%

  (Anasetti et al. *NEJM* 2012).

Prevention of GvHD

- In vitro T-cell depletion (3 randomized studies, 2 of them with CD34+ cell selection (Wagner et al. *Lancet* 2005; Pasquini et al. *JCO* 2012; Bayraktar et al. *BBMT* 2013): relapse rate=, PFS=, GvHD↓(the latter with CD34+ cell selection). Thus: probably superior to standard GvHD prophylaxis.
- In vivo T-cell depletion with ATG or alemtuzumb possibly superior to standard GvHD prophylaxis: relapse rate=, GvHD↓, OS= (in 5 studies; ↓ in 2 studies, one of them with high proportion of use of horse ATG (more toxic)). Infectious complications (ATG, alemtuzumab), PTLD (ATG). European consensus recommendation for routine use of rabbit ATG in MUD HSCT (Ruutu et al. *BMT* 2013).

Umbilical Cord Blood (UCB) SCT

- High resolution HLA matching of UCB (A, B, C, DRB1) has a major impact on non-relapse mortality (Eapen et al. *Blood* 2013).
- Maternal sensitization in use of UCB or haplo-SCT:
  - Father: P1/P2 Mother: M1/M2
  - Fetus: M1/P1

P1: inherited paternal antigen (IPA); mother gets immunized against IPA → if mother used in haplo-SCT, more GvHD & less relapse

M2: non-inherited maternal antigen (NIMA); child has tolerance towards NIMA; if T-cell depletion of haplo-HSC from father or mother, less relapse with haplo from mother; if UCB is NIMA-matched with recipient, higher survival rate than if NIMA-mismatched (→ need for maternal typing).

Acute Lymphoblastic Leukemia

ALL and Monoclonal antibodies

- Pediatric ALL: 90% cure; adult ALL (5 CALGB trials 1988-2001): overall survival (OS) at 3 yr 41% (< 30 yr 57%; 30-59 yr 38%; >60 yr 12%) → need for new approaches
- 80% of ALL: pre-B ALL → targeting by monoclonal antibodies (Mab) recognizing B-cell antigens
  - CD20: rituximab, ofatumumab
  - CD22: epratuzumab, inotuzumab ozogamicin
  - CD52: alemtuzumab
  - CD19: blinatumomab (bispecific T cell engager (BiTE) antibody); chimeric antigen receptor (CAR) transduced in (autologous) T cells

CD20 Mab in ALL

- CD20 less commonly expressed than CD19 in pre-B ALL.
- CD20+ ALL worse prognosis than CD20- ALL.
- CD20 upregulated in pre-B ALL during induction treatment.
- Modified hyper-CVAD + rituximab for 204 Ph- ALL, CD20+ on >20% blasts; non-randomized study: 'improvement' of CR duration and OS in patients <60 yr (Thomas et al. *Blood* 2009). Also increase of MRD- patients (Hoelzer et al. *Blood* 2010)
- Randomized trial ongoing (GRAALL 02/2005).
- Other CD20 Mab : eg. ofatumumab (may be more effective in killing ALL cells by ADCC).

CD22 Mab in ALL

- CD22 attractive target: expressed on >90% of B-cell malignancies, not shed in extracellular environment, not internalized (→ good candidate for immunoconjugates and immunotoxins).
- Epratuzumab (humanized naked Mab) in ALL:
  - CR=, MRD↓, DFS↑, OS↑ (Raetz et al. *JCO* 2008)
  - SWOG: clofarabine + Ara-C + epratuzumab in relapsed/refractory ALL: CR/Cri 52% (cfr. 17% in prior trial with clofarabine + Ara-C).
- Inotuzumab (ozogamicin immunoconjugate): CR/Cri 57% in relapsed/refractory ALL (of those: 63% complete molecular response and 45% went on to allo-HSCT), but grade 3-4 myelosuppression and non-hematological adverse events (Kantarjian et al. *Lancet Oncology* 2012).

Blinatumomab in ALL

- BiTE antibody, targeting CD19
- ALL patients in molecular failure/relapse after 3 cycles of chemotherapy: molecular CR (primary endpoint) was reached in 80% of cases; responses were rapid, all occurring within the first cycle, including patients with high-risk disease (eg. t(4;11), Ph+) and durable even in patients who did not go on to allo-HSCT (Topp et al. *Blood* 2010).
- Trial in relapsed/refractory adult ALL: 68% CR/Cri; 3/6 relapses: CD19- clone (Topp et al. *JCO* 2012).
- Phase III trial (ECOG): chemotherapy +/- blinatumomab post-chemotherapy-induced remission in newly diagnosed BCR/ABL-negative B-ALL in adults (40-70 yr).

CD19-CAR for ALL (published cases)

- Brentjens et al. *Sci Transl Med* 2013 (CD19.z.28): 5 adults with B-ALL (2 chemo-refractory, 2 MRD+, 1 MRD-); all MRD- after CAR; 4/5 allo-SCT; 1/5 relapse after 90 days.
- Grupp et al. *NEJM* 2013 (CD19.z.BB): 2 children with B-ALL; 1 prolonged CR, 1 transient response with $CD19^{negative}$ relapse; severe cytokine release syndrome, successfully treated with anti-IL-6R (tocilizumab)+ anti-TNFα (etanercept).
- Cruz et al. *Blood* 2013 (virus-specific T cells 19.z.28): 8 patients with B-ALL 3 mo – 13 yr post HSCT; antitumor activity in 2/6 patients with relapse.

Future of CAR: bridge to allo-HSC; remission consolidation (early MRD & pre-HSCT MRD adverse prognosis (Borowitz et al. *Blood* 2008); stand alone treatment for refractory ALL?