“Minimal Residual Disease in Hematologic Malignancies”

Leukemia Research Foundation
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Disclosure

- Honoria from Novartis and Blueprint (advisory board)
• We all want cure
• Hematologic malignancies are curable!
• However, cure requires sequential therapies
Each Phase/Cycle of Chemo/radiation therapy

- Decreases tumor burden
- Increases chance of cure
- However, some patients relapse

Boyd et al Cancer Cell 2018
AlloHCT outcomes is poor in AML patients if they are not in CR

OS  Overall 19% at 3 years

Duval M et al. J Clin Oncol 2010
Relapse is a Common Problem

Prospective Phase II HCT Study in Older AML

FLT3 AML, Graft Source, CIBMTR

Devine et al JCO 2015

Ustun et al Leukemia 2017
Treatment of Relapse is Not very Successful
What We Learned

• CR is important for success (cure)
• However, CR is not cure for most Hematologic Malignancies
• Relapse is still a common problem in patients in CR
• Treatment of relapse is difficult

• Then our goal should make sure to do everything to PREVENT relapse

• One of Most Important Thing: PREDICT Who will have a higher chance to relapse
Minimal/Measurable Residual Disease (MRD)
Detection of rare neoplastic cells (<1%) during post-treatment follow-up, by using complementary approaches:

**Multiparametric Flow Cytometry (MFC)**
Immunophenotypic analysis to detect abnormal expression of specific antigens
- Sensitivity $10^{-3} - 10^{-4}$
- Applicability >95%

**Molecular diagnostics (PCR, RT-qPCR)**
Genetic analysis to detect specific DNA signatures
- Sensitivity $10^{-3} - 10^{-6}$
- Applicability >90%

**Next Generation Flow (NGF)**
- Sensitivity $<10^{-5} - 10^{-6}$
- Applicability >99%

**Next Generation Sequencing (NGS), Digital PCR (ddPCR)**
Disease progression in AML

Bone Marrow

- **Diagnosis**
- **MRD after chemotherapy**
- **Relapse**

- Healthy stem cell
- Leukemic stem cell
- Myeloid blast
- AML blast
- Therapy resistant AML blast

Ngai et al Frontiers in Oncology 2021
MRD in Acute Lymphoblastic Leukemia

Cumulative incidence of relapse according to w10−22 MRD risk model:
- MRD Pos: ≥ 10^{-4} w10−16 and/or positive w22
- MRD Neg: < 10^{-4} w10−16 and negative w22

CR duration according to w4 (EOI) and w10 MRD:
- MRD < 10^{-4} at w4 and w10
- MRD ≥ 10^{-4} at w4 and/or w10

Sakura et al Leukemia 2018
MRD in Acute Myeloid Leukemia

130 children
Relapse;
48% high WT1 levels vs.
8% of normal WT1 levels

MRD in Multiple Myeloma in CR: A meta-analysis

A CRs only: OS hazard ratio forest plot

<table>
<thead>
<tr>
<th>Study</th>
<th>MRD Negative</th>
<th>MRD Positive</th>
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Overall HR, 0.44 95% CI, 0.34-0.56, P < .001

B CRs only: OS hazard ratio forest plot

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Overall HR, 0.47 95% CI, 0.33-0.67, P < .001

C CRs only: OS by MRD status

\[ \chi^2 \text{(ADJ)} = 42.5 \]
\[ P < .001 \]

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<th>MRD+</th>
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<td>n</td>
<td>396</td>
<td>178</td>
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D CRs only: OS by MRD status

\[ \chi^2 \text{(ADJ)} = 16.82 \]
\[ P < .001 \]

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Munshi et al JAMA 2017
Short et al Am J Hematol 2019
What We Learned

• MRD is poor prognostic

• MRD positive patients will tend to have more relapse in most (if not all) hematologic malignancies
## Methods for MRD Detection

<table>
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<th>Method</th>
<th>Case Applicability</th>
<th>Sensitivity</th>
<th>Pros and Cons</th>
</tr>
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</table>
| Karyotyping | ~50% | 1/20 | + Widely available  
+ Well-standardized  
- Slow turnaround time  
- Labor intensive  
- Requires pre-existing abnormal karyotype |
| FISH | ~50% | 1/100 | + Useful for numeric cytogenetic abnormalities  
+ Relatively quick turnaround time  
- Labor intensive  
- Requires pre-existing abnormal karyotype |
| RT-qPCR | ~40-50% | 1/10,000–1/1,000,000 | + Widely available  
+ Well-standardized  
+ Relatively inexpensive  
- Single gene assessed per assay  
- Mutations occurring outside of primer-spanning regions of gene will be missed |
| MFC | ~ All | 1/10,000–1/1,000,000 | + Widely available  
+ Relatively quick turnaround time  
+ Widely applicable  
- Not fully standardized  
- Analysis and interpretation require high-level expertise |
| NGS | >95% | 1/10,000–1/1,000,000 | + Simultaneous assessment of numerous targets  
+ Can detect mutations in any sequenced portion of a gene  
+ Very widely applicable  
- Not widely available  
- Slow turnaround time  
- Not standardized  
- Expensive (particularly to achieve high sensitivity)  
- Analysis and interpretation require high-level expertise |
Images in MM

PET/CT

WB MRI

Lecouvet et al. Skeletal Radiology 2021
How to Treat MRD? What Can we Do?

- Targeted Therapies
- Hematopoietic Cell Transplantation
- Immunotherapies
- CART cells
- Combination of all of these
What Can We Do?
-Augment Patients Own Immune System

Blincyto: how it works

T cell

GO!

CD3

Blincyto

CD19

cancer cell

Understanding Cancer Immunotherapy Research - https://www.ucir.org
Blinatumumab Induces MRD negative state and improves Outcomes

Gokbuget et al Blood 2018
How Does Hematopoietic Cell Transplantation Work?

If Donor is Patient her/himself = Autologous HCT.
Very high dose Chemo/radiation cancer cells

If Donor is another individual = Allogeneic HCT
Chemo/Radiation therapy + Other Person Immune Cells cancer cells
What Can We Do?
-Autologous HCT Bone Marrow Transplantation for consolidation of NHL

Stiff et al. NEJM 2013
What Can We Do?
- Allogeneic HCT
- Increase Intensity of Chemo/Radiation Therapy

MAC

Relapse

RIC

![Graphs showing cumulative incidence of MAC, Relapse, and RIC with P-values.](image-url)
What Can We Do?  
- Targeted Maintenance Therapy after HCT

**Diagram A**
- Censored +
- Log-rank $P = .013$
- HR, 0.39 (95% CI, 0.18 to 0.85)
- **24-month RFS**
  - Sorafenib: 85.0% (95% CI, 70% to 93%)
  - Placebo: 53.3% (95% CI, 36% to 68%)
  - Log-rank $P = .002$
  - HR, 0.256 (95% CI, 0.10 to 0.65)

**Diagram B**
- Censored +
- Log-rank $P = .0855$
- HR, 0.516 (95% CI, 0.239 to 1.112)
- **24-month OS**
  - Sorafenib: 90.5% (95% CI, 77% to 96%)
  - Placebo: 66.2% (95% CI, 49% to 79%)
  - Log-rank $P = .007$
  - HR, 0.241 (95% CI, 0.08 to 0.74)

**No. at risk:**
- Placebo 40 24 19 17 14 0
- Sorafenib 43 35 31 25 18 0

**No. at risk:**
- Placebo 40 25 19 9 3 0
- Sorafenib 43 38 28 12 7 0

Burchert et al J Clin Oncol 2020
What Can We Do?
Augment Patient Own Immune Cells (in the body)
- PDL-1 inhibitors
What Can We Do?
Augment Patient Own Immune Cells (in the body)
- PDL-1 inhibitors (Pidilizumab) after autologous HCT for NHL

All Patients
Residual Disease+ before autoHCT

Residual Disease+ After autoHCT
N=35 patients
ORR=51%
CR=34%

Armand et al J Clin Oncol 2013
What Can We Do?
-Augment patient Own Immune Cells (out of Body)
What Can We Do?

- CART cells
- Augment patient Own Immune Cells (out of Body)

Lu et al Cancer Immunol Immunotherapy 2021
Conclusions

• MRD helps us to tailor treatment for individual patient

• Therefore we can prevent relapse in patients who needs more therapy
• We can also decrease unnecessary t

• MRD detecting tecniques have been improving

• Treatment of MRD “arsenal” has been expanding