Chronic lymphocytic leukemia

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Chronic lymphocytic leukemia

- Acronym: CLL

- clonal expansion of mature B-lymphocytes in blood and lymphoid organs (BM, lymph nodes, spleen)

- rarely without blood and BM involvement, then termed "small lymphocytic lymphoma" (SLL)

- 1st noticed by Rudolf Virchow 1845
...and its exotic relatives

- **T-PLL**: T-Prolymphocytic leukemia - a rare aggressive disorder
- **T-CLL**: is now T-PLL (marked for removal)
- **B-PLL**: B-Prolymphocytic leukemia - hard to separate from aggressive CLL
- **HCL**: hairy cell leukemia - an indolent B cell lymphoma with nowadays a very good prognosis and, thus, a very rare transplant indication
Newly developed defect in the genetic program of a single mature B-lymphocyte.
CLL: Development

Newly developed defect in the genetic program of a single mature B-lymphocyte -

→ cell loses ability to switch off itself (Apoptosis)

→ expands and accumulates over time in
  - Blood
  - Bone marrow
  - Lymph nodes
  - Spleen
CLL: Course

Two principle possibilities:

1. Equilibrium between expansion and natural die-off of CLL cells
   → few symptoms, good prognosis

2. No equilibrium; ongoing increase of CLL cell numbers;
   → Overgrowth of lymphoid organs, symptoms, poor prognosis
CLL: Symptoms

- often none!
  - unspecific: sweats, fever, weakness
  - lymph node enlargement
  - spleen enlargement
  - anemia, thrombopenia
  - infections

Blood lymphocytosis does not cause symptoms!
CLL: Binet and Rai Staging

Median survival (in the old days)

Binet A, Rai 0-1: 5 to >15 years

Binet B, Rai 2: 5 years

Binet C, Rai 3-4: 2.5 years

dead from infections, BM failure, high-grade transformation (Richter's syndrome), cachexia
Richter’s Syndrome

- is always the transformation of CLL into an aggressive Lymphoma - diffuse large cell lymphoma (DLCL) or Hodgkin‘s lymphoma
- usually evolves after a long indolent course -
- can occur as 1st manifestation of CLL: Primary Richter‘s - but still CLL
- has a poor prognosis
Richter’s Syndrome

**SPECIFICATIONS OF THE DISEASE**

**CHRONIC LYMPHOCYTIC LEUKAEMIA (AND OTHER LYMPHOCYTIC LEUKAEMIAS)**

**INITIAL DIAGNOSIS**

Has the information requested in this section been submitted with a previous HSCT registration?
- Yes: go to “Pre-HSCT treatment” on page 2
- No: proceed with this section

**SUBCLASSIFICATION**

- Chronic Lymphocytic Leukaemia (CLL) / Small Lymphocytic Lymphoma (SLL)
- Prolymphocytic Leukaemia (PLL)
  - PLL, B type
  - PLL, T type
- Richter’s syndrome:
  - Transformed from CLL
  - No (Primary Richter)
  - Yes
- Hairy Cell Leukaemia (HCL)
- Atypical Hairy Cell Leukaemia
- Other, specify ..........................................................

How to code ”Primary Richter’s“ in MedB
Genomic Aberrations in CLL detected by FISH

17p-  13q-  +12q13

Genomic aberrations found in approximately 80% of CLL

Döhner et al 2000
CLL: FISH and survival

Survival from Time of Diagnosis (n=325)

Survival in Months

- 17p-
- 11q-
- +12
- 13q- single

Döhner et al 2000
CLL: Ig (VH) gene status

CLL cells as mature B-lymphocytes express immunoglobulines (Ig) on the cell surface -

Bone marrow ↔ Blood, lymph

Ig can be in a mutated or unmutated status.
VH gene status and prognosis

Stage A CLL

VH mutated
(n=106)

VH unmutated
(n=83)

% survival

months

Kröber et al 2002
ZAP70 is an intracellular protein which is strongly correlated with the VH status in CLL. Therefore it is used as prognostic marker.

Crespo et al 2003
**MedB: Biological RF assessment**

### Biological Risk Factor Assessment

**Cytogenetics**
- [x] Not done or failed
- [ ] Normal
- [x] Abnormal
- [ ] Unknown

**Technique**
- [x] Conventional
- [x] FISH
- [ ] Both
- [ ] Unknown

**Abnormalities (if present)**
- [ ] Trisomy 12
- [x] Del 13q14
- [x] t(11;14)
- [x] Del 11q23
- [x] Del 17p53
- [ ] Del 13q14
- [ ] Other: ..................................

**VH gene status**
- [x] Not mutated
- [ ] Mutated

**IF EVALUATED: VH3-21 status**
- [x] Not used
- [x] Used

**MARKERS**
- [x] Absent
- [x] Present: ZAP-70 Expression cut-off used: 20%
- [ ] Other, specify ............

**Molecular or other type of markers**
- [x] Not evaluated
- [ ] unknown

---

*a CLL patient with a very poor prognosis*
**BIOLOGICAL RISK FACTOR ASSESSMENT**

**CYTOGENETICS**
- □ Not done or failed
- ☑ Normal
- □ Abnormal
- □ Unknown
- □ Conventional
- □ FISH
- □ Both
- □ Unknown

**Abnormalities (if present)**
- □ Trisomy 12
- □ Del 13q14
- □ Del 11q23
- □ Del 17p53
- □ t(11;14)
- □ Other: ................................

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**IF EVALUATED:**
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- □ Not used
- □ Used
- □ Not evaluated
- □ unknown

**MARKERS**
- ☑ Absent
- □ Present:
  - ☑ ZAP-70: Expression cut-off used: 20%
  - □ Other, specify ..............
- □ Not evaluated
- □ unknown

---

A CLL patient with a better prognosis
CLL: Prognosis

Median survival (with chlorambucil)

Binet A, Rai 0-1: 5 to >15 years

Binet B, Rai 2: 5 years

Binet C, Rai 3-4: 2.5 years

Nobody could be cured!
Looking out for better treatment:

Along came the *purine analogues*.

- Fludarabine
- Cladribine (2-CDA)
- Pentostatin
Better PFS with fludarabine

PFS: F > CLB

Rai et al 2000
How to improve on fludarabine?

Combination of fludarabine with

• Cyclophosphamide ("FC" regimen)
Better PFS with FC

Eichhorst et al 2006

PFS GCLLSG CLL4 trial (1st-line)

62 months

Months from randomization

Cum progression-free

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 6 12 18 24 30 36 42 48 54 60 66 72 78

RANDOM

FC

FC-censored

F

F-censored

Eichhorst et al 2006
How to improve on fludarabine?

Combination of fludarabine with

• Cyclophosphamide ("FC" regimen)
• Antibodies - Rituximab ("FC-R" regimen)
What is an “antibody”?  

Rituximab

- human immunoglobuline
- reshaped to bind to the CD20 Antigen exclusively expressed on B cells
- kills cells from outside
- trade name: Mabthera
How to improve further?

Still no cure - what about transplant?
How does chemotherapy work?

- Chemoth.
- Auto-SCT
- Allo-SCT
- "mini-SCT"

Tumor control

- Antibody
- Drugs
- Radiotherapy
- GVL
How does auto-SCT work?

- Chemoth.
- Auto-SCT
- Allo-SCT
- "mini-SCT"

Tumor control

- Antibody
- Drugs
- Radiotherapy
- GVL
Can auto-SCT cure CLL?

EBMT 2005

n = 1323

Dreger, Brand et al 2007
Minimal residual disease (MRD)

MRD is a level of tumor load which is too small to be detected by clinical methods (microscopy etc.)

2 methods for MRD assessment which can detect at least 1 CLL cell in 10,000 normal leukocytes:

1. 4-colour flow cytometry ("Immunophenotyping")

2. Clone-specific PCR ("Molecular Biology")
MRD after auto-SCT (CLL3 trial)

Ritgen et al 2004
Reporting of MRD response

BEST DISEASE RESPONSE AT 100 DAYS POST-HSCT

- CR
- PR
- No response
- Progression
- Unknown

DATE OF EVALUATION: yyyy mm dd

RESIDUAL DISEASE STATUS (ONLY TO BE COMPLETED WHEN PATIENT IS IN HAEMATOLOGICAL COMPLETE REMISSION)

Minimal residual disease investigated by:
- Immunophenotyping: Negative, Positive, Not evaluated, Unknown
- Molecular Biology: Negative, Positive, Not evaluated, Unknown

Please indicate sensitivity of MRD assay: 10⁻⁵ = 1 in 100,000

The usual result of MRD testing after auto-SCT for CLL
Can auto-SCT cure CLL?

No.
How to achieve cure in CLL?

Still no cure with auto-SCT - what about allo-SCT?
How does allo-SCT work?

- Antibody
- Drugs
- Radiotherapy
- GVL

Tumor control

- Chemother.: Antibody, Drugs
- Auto-SCT: Antibody, Radiotherapy
- Allo-SCT: Antibody, Drugs, Radiotherapy, GVL
- "mini-SCT":
GVL in CLL: Survival plateau

International Project on CLL

Auto  63% (±7)

(100d allo-TRM 31%)

Allo  56% (±7)

Esteve et al 2001
GVL in CLL: DLI effective

Ritgen et al 2008

MRD level

1E+6
1E+5
1E+4
1E+3
1E+2
1E+1
1E+0
1E-1
1E-2
1E-3
1E-4
1E-5
1E-6

days

0 200 400 600 800 1000

CSA taper

DLI

Ritgen et al 2008
Rationale for RIC in CLL

If GVL is the main effector - do we need full conditioning?

→ Reduced-intensity conditioning (RIC)
How does RIC-SCT work?

Chemoth.
Auto-SCT
Allo-SCT
RIC-SCT

Tumor control

Antibody
Drugs
Radiotherapy
GVL
Immunomodulation and MRD kinetics: Results of GCLLSG CLL3X trial
CLL3X: Patient flow (MRD)

113 ineligible (no CLL, late registration, comorbidity etc.)
100 no SCT (Richter’s, ED, no donor, refusal)
90 no continuous MRD sampling
52

13 event <12mo,
27 MRD-neg at +12mo
11 MRD-pos at +12mo
1 no MRD at +12mo
CLL3X: Clinical impact of MRD negativity at +12mo
(of 38 patients with MRD monitoring and event-free at mo +12)

Dreger et al, GLLSG 2009
## Reporting of MRD response

### LAST DISEASE AND PATIENT STATUS

<table>
<thead>
<tr>
<th>Last Disease Status</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Complete Remission</td>
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</tr>
<tr>
<td>Stable disease</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td></td>
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</table>

### Residual Disease Status

(Only to be completed when patient is in Haematological Complete Remission)

Minimal residual disease investigated by:

<table>
<thead>
<tr>
<th>Method</th>
<th>Negative</th>
<th>Positive</th>
<th>Not Evaluated</th>
<th>Unknown</th>
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<tbody>
<tr>
<td>Immunophenotyping</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Biology</td>
<td></td>
<td>✔</td>
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</tr>
</tbody>
</table>

Please indicate sensitivity of MRD assay:

- \(10^{-4} = 1 \text{ in } 10,000\)

A frequently observed result of MRD testing after allo-SCT for CLL
Reporting of clinical response is done according to the 2008 iwCLL guidelines - look up the 2008 MedB CLL manual!
Who with CLL needs allo-SCT?

Even RIC-SCT is still a risky procedure - indicated only in high-risk disease.
allo-SCT is a reasonable treatment option in poor-risk CLL:

- Relapse <24 mo after intensive treatment (purine analogue combinations or auto-SCT)
- p53 mutation with treatment indication
- Non-response or early relapse (<12 mo) after purine analogue-based therapy (= fludarabine resistance)

Still valid in 2010!

Leukemia 21:12-17 (2007)
**CLL: Outcome of patients refractory to purine analogues**

Alemtuzumab therapy (GCLLSG CLL2H trial); n=103

- **Time to treatment failure**
  - Median: 5.6 mo.

- **Overall survival**
  - Median: 19.1 mo

*Stilgenbauer et al, JCO 27:3394 (2009)*
CLL: Survival of patients refractory to purine analogues

Alemtuzumab therapy (GCLLSG CLL2H trial); n=103

Stilgenbauer et al, JCO 27:3394 (2009)
allo-SCT is a reasonable treatment option in poor-risk CLL:

- Relapse <24 mo after intensive treatment (purine analogue combinations or auto-SCT)
- p53 mutation with treatment indication
- Non-response or early relapse (<12 mo) after purine analogue-based therapy (= fludarabine resistance)
Reporting a patient with short response to PA combination therapy

<table>
<thead>
<tr>
<th>Purine analogue-refractory?</th>
<th>☑ No</th>
<th>☐ Yes</th>
<th>☐ Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>(non response or relapse within 6 months after completion of purine analogue-containing chemotherapy)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early relapse after intensive therapy?</th>
<th>☐ No</th>
<th>✓ Yes</th>
<th>☐ Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>(within 24 months after completion of purine analogue-containing combination therapy or autologous SCT)</td>
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</tbody>
</table>

Patient who relapsed 18 months after fludarabine-cyclophosphamide-rituximab combination (FC-R)

Dreger et al 2007
Is allo-SCT effective in PA-ref. CLL?

Relapse by F resistance

CLL3X trial
n = 80

Percent relapsed

Months from SCT

HR .94 (.35-2.5)

Dreger et al 2007
Is allo-SCT effective in 17p- CLL?

EBMT survey
n = 44

3-y PFS 44% (95% CI 28% to 60%)

Schetelig et al 2008
Can allo-SCT cure CLL?

Yes!
Finally -

Ready for your questions!
Thank you!

CLL3X trial
S Stilgenbauer
M Ritgen
S Böttcher
D Beelen
S Cohen
J Schubert
N Schmitz
M Hallek
H Döhner

Consensus
P Corradini
M Hallek
E Kimby
M Michallet
D Milligan
W Wiktor
E Montserrat

p53
A van Biezen
R Brand
D Caballero
J Schetelig

... and Shelley Hewerdine for invitation!