AL AMYLOIDOSIS

SAMO November 2015 Lucerne

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amyloidosis

- diagnosis
- pathophysiology
- prognosis
- therapy
- perspectives
amyloidosis

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diagnosis

Amyloidosis registry ZH GR (n=105)

- ? 10%
- AA 29%
- AL 23%
- AL (klin) 8%
- TTR-FAC 2%
- TTR-FAP 2%
- wtATTR 4%
- ATTR (klin) 8%
- ATTR (Szinti) 2%
diagnosis

- think of it!
- delay from symptoms to diagnosis > 1 year. Often > 5 physicians consulted\(^1\)
- MGUS patients follow-up
  - albuminuria (> 0.5g/24h)
  - NT-ProBNP (>332 pg/l) or BNP >73 ng/L
- tongue enlargement and raccoon eyes are typical for AL
- heart failure (hypertrophy), neuropathy, nephrotic syndrome

\[^1\text{Lousada Adv Ther. 2015}\]
diagnosis

- genetic testing in known hereditary amyloidosis (e.g. TTR)
- In AL amyloidosis fine needle biopsy of the abdominal fat and bone marrow biopsy can have a high sensitivity\(^1\)
- typing of amyloid deposits crucial
  - general population: MGUS 5.3% >70 years, 7.5% ≥85 years\(^2\)
  - 25% pat. with hereditary amyloidoses and wtTTR amyloidosis have an MGUS\(^3,4\)
  - misdiagnosis is common (10% )\(^3\)
  - MS-based proteomics ,gold-standard\(^5\)
    ... but not available in CH
- Tc-DPD-scintigraphy pos. in TTR not in AL\(^6\)

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Misfolding:
- Intrinsic instability
- Mutations
- ↑ concentration
- Proteolysis
- Aging

Interaction with tissue microenvironment:
- Proteases
- Collagen, GAGs, SAP
- Metal ions

Amyloid deposits

Amyloid precursor

Misfolded protein

Oligomers

Organ dysfunction

Proteostasis
- Extracellular chaperones

courtesy of Mario Nuvolone PhD USZ
pathophysiology

-> beta sheet structure

courtesy of Mario Nuvolone PhD USZ
pathophysiology

- not only amyloid aggregates are toxic but also soluble LC

- in vivo
  - clinical improvement in patients achieving CR despite unchanged echocardiographic findings

- in vitro: toxicity of circulating soluble light chains: Activation of p38 mitogen-activated protein kinase (MAPK)\(^1\), stanniocalcin1 (STC1) overexpression\(^2\), amongst others\(^3-5\)
  - oxidative stress -> mitochondrial damage -> apoptosis of cardiomyocytes
  - selective cardiotoxicity (organ tropism) depends on LC sequence, e.g. few amino acid differences of 2 recombinant LCs derived from the same germline gene (\(I\text{GLV1-44}\)) exhibit either cardiac or non cardiac toxicity\(^4,5\)

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\(^1\) Shi PNAS 2010, \(^2\) Guan Basic Res Cardiol 2013, \(^3\) Lavatelli FASEB J 2015, \(^4\) Diomede Worm 2014, \(^5\) Diomede Blood 2014
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# prognosis

largely depends on the heart (and the tumor burden)$^1$

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>NT-ProBNP</td>
<td>$\geq 1800$ pg/mL</td>
</tr>
<tr>
<td>cardiac Troponin T (cTdT)</td>
<td>$\geq 0.025$ ng/mL</td>
</tr>
<tr>
<td>difference (not the ratio) of the free serum light chains (involved - non involved) = dFLC</td>
<td>$\geq 180$ mg/L</td>
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</table>

One point for every positive marker

$\rightarrow$ Stage 4 (3 points) – Stage 1 (0 points)

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$^1$Kumar JCO 2012
prognosis

B

Overall Survival (proportion)

Follow-Up From Diagnosis (months)

No. at risk
512
335
255
176
119
64

Kumar JCO 2012
very poor prognosis

- Stage III amyloidosis with NT-ProBNP >8500 pg/ml are at high-risk of very early death (weeks)
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therapy

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Interaction with tissue microenvironment:
Proteases
Protease inhibitors
Collagen, GAGs, SAP
Metal ions

Amyloid precursor
Misfolded protein
Oligomers
Organ dysfunction
Amyloid deposits

Chemotherapy
Organ transplantation
siRNA
Anti-sense oligonucleotides

Supportive care
Organ transplantation

Anti-SAP antibodies
CPHPC
SAP
GAGs
GAGs mimetics

Immunotherapy

Proteostasis
Extracellular chaperones

courtesy of Mario Nuvolone PhD USZ

SAMO 6th November 2015
amyloidosis
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therapy – general remarks

- depends on the condition of the patient and the pattern of organ involvement

- general remarks:
  - chemotherapy is often not well tolerated
  - frequent dose adjustments are necessary
  - change treatment approach early if it proves to be ineffective (serum free light chains have a very short half-life, unlike IgG)
  - If possible instruct your patients to monitor vital signs/weight
    - e.g. diuretic dose adjustment
    - blood pressure
therapy – general remarks

- **Bortezomib (V):**
  - subcutaneous administration recommended.
  - preexisting neuropathy is most important risk factor for neurological toxicity
  - If a fast response is needed, start bi-weekly (cycle 1-2)

- **Dexamethasone (D):**
  - poorly tolerated in severe heart disease and/or nephrotic syndrome (volume overload)
  - arrhythmia

- **Cyclophosphamide (C):**
  - infectious complications

- **Lenalidomide (R):**
  - cardiac marker elevation, arrhythmia (combination with D)
therapy – goals

- hematologic response (fast)$^1$: at least VGPR

<table>
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<tr>
<th>CR</th>
<th>normal FLC ratio and negative serum and urine immunofixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>difference between involved and uninvolved FLCs [dFLC] &lt; 40 mg/L</td>
</tr>
<tr>
<td>PR</td>
<td>dFLC decrease &gt;50%</td>
</tr>
<tr>
<td>NR</td>
<td>dFLC decrease &lt;50%</td>
</tr>
</tbody>
</table>

- organ response (needs patience)$^{1-3}$:
  - n=313 all had normalization of the FLC ratio after therapy
  - 80% organ response within 1 year
  - the earlier the response the better the OS

$^1$Palladini JCO 2012, $^2$Kaufmann AJH 2015, $^3$Palladini Blood 2014
therapy

high dose therapy with melphalan and ASCT yes or no?

- only about 15-20% of all patients eligible
- Yes, if
  - age < 70 years
  - NYHA stage < III
  - ECOG (WHO) performance status < 3
  - systolic BP standing > 100 mmHg
  - cTroponin T <0.06 ng/mL or NT-proBNP <5000 pg/ml

  (not on dialysis)

- no symptomatic effusions
- creatinine-clearance > 30-50 ml/min or on dialysis

1adapted from Dispenzieri Mayo Clin Proc. 2015, Merlini JCO 2011; 2Gertz Bone Marrow Transplant. 2013
high-dose therapy

- no benefit vs. Mel/Dex<sup>1</sup>
  - TRM 24%, centers with only 1 TPL, longer time to TPL than to Mdex, NYHA III-IV patients included
  - in non specialized centers MelDex better than HD-therapy
- Benefit (long-term follow-up)<sup>2</sup>
  - Especially in patients in CR one year after TPL

- TRM in newer studies 4 - 12%<sup>3-6</sup>

<sup>1</sup>Jaccard NEJM 2007,<sup>2</sup>Sanchorawala Blood 2015,<sup>3</sup>Sanchorawala BMT 2013,<sup>4</sup>Kongtim BMT 2015,<sup>5</sup>Venner Haematologica 2014,<sup>6</sup>Hazenberg HOVON-41 Haematologica 2015
therapy

- high-dose therapy – some practical considerations
  - talk about ICU admission and resuscitation measures and make sure you follow the patients will
  - discontinue ACE-I prior to admission
  - do not use nephrotoxic drugs (e.g. i.v. contrast media)
  - monitor volume status very carefully and adjust diuretics early
  - monitor electrolyt levels carefully and replace them
  - better start anti-infective treatment early, you can still discontinue later if not needed
  - patients with cardiac disease are at risk for arrythmia, and tolerate e.g. atrial fibrillation poorly. Treatment of choice is most often amiodarone but contact your cardiologist
therapy

do we need induction prior to HD-therapy?

- makes sense if it works (clearance of toxic light chains)
- don’t lose time if it doesn’t work

- Vd (bi-weekly) induction followed by V-MEL200 and ASCT\(^1\)
  - 35 patients (5 did not undergo ASCT): ITT HR in 77% of patients

- VAD Induction followed by MEL200 and ASCT\(^2\)
  - 69 patients: 18% patients died during induction with VAD
  - ITT median OS 96 months, in patients with HD and ASCT 10 years

- VD/VCD induction enabled 33% (n=8) of initially transplant ineligible patients to undergo HD therapy and ASCT\(^3\)

- Randomized Trial VD + HD/ASCT vs only HD/ASCT (n=56)\(^4\)
  - 2y OS 95% vs 69.4% in the HDM/SCT alone group (p = 0.03).

\(^1\)Sanchorawala BBMT 2015, \(^2\)Hazenberg HOVON-41 Haematologica 2015, \(^3\)Cornell BMT 2015, \(^4\)Huang BMC Med 2014
therapy

trial results difficult to interpret and compare
- few prospective trials
- different end points (hematologic response, organ response)
- Mixed population (front-line, second-line)

Single-agent (a selection)
- Dexamethasone (n=91): Phase II 55% ORR Dhodapkar *Blood* 2004
  - 3 cycles of Dex 40 mg/d d1-4, 9-12, and 17-20, every 35d
- Bortezomib (n=31): Phase I/II, 50% ORR Reece *Blood* 2009
therapy

doublets (a selection)

- Melphalan/Prednisone (n=77): ORR 29% Kyle NEJM 1997
- Bortezomib/Dexamethasone (n=91): ORR 71% Kastritis JCO 2012
- Thalidomide/Dexamethasone (n=31): ORR 48% Palladini Blood 2005
- Lenalidomide/Dexamethasone (n=22). ORR 41% Dispenzieri Blood 2007

- Melphalan/Dexamethasone
  - ORR 67% (n=46) Phase II Pelladini Blood 2004
    - Mel 0.22 mg/kg + Dex 40 mg orally d1-4 every 28d
  - ORR 68% (ITT 52%) (n=50) Phase II Jaccard NEJM 2007
    - Mel 10 mg/m² and Dex 40 mg orally on d1-4 every 28d
therapy

V-based triplets

- **VCD (n=230):** Palladini *Blood* 2015 - retrospective pooled data
  - Overall hematologic response rate in the 201 patients with measurable disease 62%
  - 17% cardiac response, renal response in 25%

- **However V is not not very effective in t(11:14):** Bochtler *JCO* 2015
  - VD n = 101, VCD n = 32 (retrospective)
  - Inferior hematologic event-free survival vs absence of t(11:14) median, 3.4 v 8.8 months, p= .002
  - Overall survival (median 8.7 v 40.7 months, p= .05)
  - Remission rate (≥ very good partial remission; 23% v 47%, p= .02)
therapy

V-based triplets

- **VMD vs MD (n=174):** Palladini *Leukemia* 2014 – retrospective matched case control
  - V benefit in patients < NYHA III and with NT-ProBNP < 8500 ng/l
  - V without benefit if high-dose Dexemethasone is tolerated

- **VMD vs MD - EMN-003 trial (NCT01277016) (n=110):** IMW 2015
  Rome no significant benefit of VMD (PFS, OR) after 19 months.

- **VCD vs VTD (n=138):** Venner *Leukemia* 2014 – retrospective matched case control
  - ORR 71.0% vs 79.7% (p=0.32).
  - CR rate 40.5% vs 24.6% (p=0.046).
  - One-year OS 65.2% and 66.7% (p=0.87).
  - PFS 28.0 and 14.0 months (p=0.039).
therapy

R-based triplets

- **RCD (Phase II) n=26**: Cibeira *BJH* 2015 – prospective single arm
  - 46% ORR

- **RMD (Phase II) n=25**: Dinner *Haematologica* 2013
  - ORR 58%
  - 33% of cardiac arrhythmias
  - treatment completion 12.5%
what would I do - transplant eligible

- VCD
  - after 2 cycles
    - response: continue for up to 3 or 4 cycles and collect stem cells
    - no response: Collect stem cells and proceed to HD therapy and ASCT
  - after 3-4 cycles
    - CR: discuss consolidation with HD therapy and ASCT
    - <CR: proceed to HD therapy and ASCT

- HD therapy with MEL dose adjustment if CCr < 50ml/min and/or dialysis and/or patient >65y old (100 – 140 mg/m²)

- Consolidation 2-3 months after HD-Therapy if not in CR
  - repeat induction drug combination if an ongoing efficacy had been observed. If not -> change
what would I do - transplant ineligible

comorbidities guide treatment decision

- first-line VCD (3 cycles)
  - if at least VGPR reached -> continue for 1-2 cycles beyond best response
  - if only PR reached -> continue for 1 more cycle and then switch if no further improvement has been obtained
  - if < PR -> switch treatment

- second-line MelDex (3 cycles) especially in t(11;14)
  - if at least VGPR reached -> continue for 1-2 cycles beyond best response
  - if only PR reached -> continue for 1 more cycle and then switch if no further improvement has been obtained
  - if < PR -> switch treatment

- third-line treatment
  - Lenalidomid or Bendamustin based
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perspectives

- myeloma drugs (incl Abs and oral PI, ABT-199)
- stabilize the heart
  - p38MAPK inhibitors
  - doxycyclin
  - epigallocatechin-3-gallate (EGCG) Mereles *Clin Res Cardiol.* 2010
    
z.B. Alpinamed oder Phytopharma 4x300mg/d
- remove amyloid
  - small molecules against SAP + antibodies against SAP Richards *NEJM* 2015
  - other Abs against amyloid deposits
- suppress production (siRNA) Zhou *Blood* 2014
- specialized treatment centers (z.B. USZ)
  
Thank you