Update in Hematology
14th SIOG meeting
Lisboa, October 23rd, 2014

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(Hematology and Oncology)

Innsbruck Medical University

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## Disclosures – Reinhard Stauder

<table>
<thead>
<tr>
<th>Role</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Celgene, Novartis, Teva</td>
</tr>
<tr>
<td>Employee</td>
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</tr>
<tr>
<td>Consultant</td>
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</tr>
<tr>
<td>Major Stockholder</td>
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<tr>
<td>Honoraria</td>
<td>Celgene, Novartis, Teva</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>Celgene</td>
</tr>
</tbody>
</table>
Hematologic malignancies in elderly

KEY POINTS

- Integration of elderly in clinical studies
- Definition of appropriate endpoints
- Integration of geriatric assessment
  - Risk scoring?
  - Therapy planning and prediction of toxicity?

*Based on Lichtman S. 13th SIOG Meeting Copenhagen 2013 & Wildiers H. et al., JCO 2013*
Predictive model for chemotherapy toxicity
Predominantly solid tumors

Ability of (A) risk score versus (B) physician-rated Karnofsky performance status (KPS) to predict chemotherapy toxicity.

Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score defines risk levels of severe toxicity.

Hurria A. et al., JCO 2011
Extermann M. et al., Cancer 2012
### Hematologic malignancies in elderly - Relevance

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Median age at diagnosis</th>
<th>Publications PubMed 2013/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic Syndromes (MDS)</td>
<td>75</td>
<td>36</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>75</td>
<td>87</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>70</td>
<td>111</td>
</tr>
<tr>
<td>Diffus large B-cell NHL (DLBCL)</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Chronic lymphatic leukemia (CLL)</td>
<td>70</td>
<td>41</td>
</tr>
<tr>
<td>Myeloproliferative neoplasms (PMN)</td>
<td>PMF 67, ET 60, CML 50</td>
<td>15</td>
</tr>
<tr>
<td>M. Hodgkin: two peaks in age distribution</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia (ALL): two peaks</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

1 Based on Tumor registry Tyrol ([www.iet.at](http://www.iet.at)) and SEER
2 based on PubMed search using the term «elderly», performed Oct 18th, 2014
Prognostic factors for mortality
Search results and study selection

- All studies: n=1487
  - Medline: n=677
  - Embase: n=810

- Duplicates: n=56

- Exclusion: n=1413
  - Not original research: n=154
  - Not haematological malignancies: n=837
  - No geriatric assessment (GA): n=393
  - Retrospective GA: n=3
  - Insufficient data in abstract: n=3
  - No relevant outcome measures: n=1
  - Conference abstract for which full text later became available: n=10
  - Patient selection by GA: n=5
  - Treatment stratified by GA: n=7

- Inclusion: 18 publications from 15 studies
- Cross referencing yielded no additional studies

## Prognostic factors for mortality

### Hematological malignancies in the elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Results univariate analyses</th>
<th>Results multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author</td>
<td>Year of publication</td>
</tr>
<tr>
<td></td>
<td>Klepin</td>
<td>2013 (2011)</td>
</tr>
<tr>
<td></td>
<td>Deschler</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>Corsetti</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Tucci</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Soubeyran</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Winkelmann</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Rollot-Trad</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>Soubeyran</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>Wedding</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Wildes</td>
<td>2013</td>
</tr>
</tbody>
</table>

| Proportion of studies with a significant association (%) | 57 | 71 | 50 | 50 | 55 | 83 | 20 | 100 | 67 | 14 | 29 | 50 | 14 | 14 | 20 | 0 | 75 | 67 |

Based on a systematic Medline and Embase search, June 21st 2013

Clinical studies in hematological malignancies in elderly
Search results and trial selection

- United States National Institutes of Health (NIH) clinical trial registry
- Search on July 1st 2013, for currently recruiting phase I, II or III clinical trials in hematological malignancies
- Trial characteristics and study objectives were extracted from the registry website

<table>
<thead>
<tr>
<th>Search yield</th>
<th>n=39,376</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion</td>
<td>n=38,168</td>
</tr>
<tr>
<td>Observational trials</td>
<td>n= 6,073</td>
</tr>
<tr>
<td>Not phase I, II or III</td>
<td>n= 10,707</td>
</tr>
<tr>
<td>Unknown recruitment status</td>
<td>n= 3,529</td>
</tr>
<tr>
<td>Not recruiting</td>
<td>n= 13,329</td>
</tr>
<tr>
<td>Study includes (only) solid malignancies</td>
<td>n= 4,531</td>
</tr>
</tbody>
</table>

Inclusion: n=1,207

### Exclusion of older patients by diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>On-going clinical trials</th>
<th>Trials excluding older patients (%)</th>
<th>Trials excluding older patients based on age (%)</th>
<th>Trials excluding older patients based on performance status (%)</th>
<th>Trials excluding older patients based on organ function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>49</td>
<td>88</td>
<td>67</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>36</td>
<td>69</td>
<td>44</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>46</td>
<td>72</td>
<td>22</td>
<td>11</td>
<td>63</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>122</td>
<td>61</td>
<td>16</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>135</td>
<td>78</td>
<td>42</td>
<td>19</td>
<td>49</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>196</td>
<td>63</td>
<td>19</td>
<td>19</td>
<td>48</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>64</td>
<td>67</td>
<td>17</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>81</td>
<td>56</td>
<td>6</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>Overall</td>
<td>1207</td>
<td>69</td>
<td>27</td>
<td>16</td>
<td>51</td>
</tr>
</tbody>
</table>

Trials were considered to be excluding elderly patients based on age if they used an upper age limit of ≤75 years.

Clinical studies in hematological malignancies in elderly

Summary

Conclusion

- Only 5% of trials focused exclusively on elderly and frail.
- 69% of trials excluded older patients.
  - Exclusion
    - based on age in 27% (*the heterogeneity of the elderly population does not legitimize exclusion based on chronological age alone*).
    - based on performance status in 16%
    - based on stringent organ function restrictions in 51%.
- Over time, there was a shift from exclusion based on age toward exclusion based on organ function.

*Hamaker M. et al, The Oncologist, 2014*
Clinical trials in elderly patients with a hematological malignancy: are we addressing the right end-points?

<table>
<thead>
<tr>
<th>End-point</th>
<th>Trials exclusively for elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>71%</td>
</tr>
<tr>
<td>Efficacy</td>
<td>76%</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>66%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>58%</td>
</tr>
<tr>
<td>Biological parameters</td>
<td>10%</td>
</tr>
<tr>
<td>Pharmacological parameters</td>
<td>15%</td>
</tr>
<tr>
<td>Quality of life</td>
<td>18%</td>
</tr>
<tr>
<td>Health care utilization</td>
<td>7%</td>
</tr>
<tr>
<td>Completion of treatment</td>
<td>3%</td>
</tr>
<tr>
<td>Functioning</td>
<td>2%</td>
</tr>
</tbody>
</table>

Hematologic malignancies in elderly

Distinct entities

- Key points and selected manuscripts 2013/2014
- Selection is subjective
Hematological malignancies - DLBCL

KEY POINTS

- Decision making in DLBCL represents a paradigm of decision making in geriatric oncology; who is eligible for curative treatment?
- SIOG Task force DLBCL (Morrison V) guidelines are submitted (JGO, Ann Oncol) SIOG-guideline session on Saturday

RELEVANT PUBLICATIONS

- Relevance of nutritional situation is highlighted by
  - Aaldriks AA et al., Leuk Lymphoma, 2014, risk of malnutrition, based on MNA has a predictive value for early treatment withdrawal.
  - Melchardt T et al. Br J Hem 2014; Albumin was retained as an independent prognostic factors for survival in a multivariate analysis.
  - Camus V et al., Eur J Haematol. 2014 Prognostic impact of fat tissue loss and cachexia assessed by CT-scan in elderly patients with DLBCL treated with immunochemotherapy.
  - Lanic H et al., Leuk Lymphoma 2014 Sarcopenia is an independent prognostic factor in elderly patients with DLBCL treated with immunochemotherapy
  - Tucci A. et al, Leuk Lymphoma 2014; CGA was very efficient in identifying elderly patients with DLBCL who can benefit from a curative approach.
  - Marchesi F et al., JGO, 2013: Patients classified as “fit” and “intermediate” who were receiving curative treatments presented with a significantly better OS when compared with those treated conservatively on the basis of clinical judgment.
Hematological malignancies - DLBCL

KEY POINTS

- Decision making in DLBCL represents a paradigm of decision making in geriatric oncology; who is eligible for curative treatment?
- SIOG Task force DLBCL (Morrison V) guidelines are submitted (JGO, Ann Oncol) SIOG-guideline

RELEVANT PUBLICATIONS

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  - Lanic H et al., Leuk Lymphoma 2014 Sarcopenia is an independent prognostic factor in elderly patients treated with immunochemotherapy.
  - Tucci A. et al, Leuk Lymphoma 2014; CGA was very efficient in identifying elderly patients with a curative approach.
  - Marchesi F et al., JGO, 2013: Patients classified as “fit” and “intermediate” who were receiving curative treatments presented with a significantly better OS when compared with those treated conservatively or palliatively.
New targets and therapeutic agents in CLL

Hematological malignancies
Chronic lymphatic leukemia (CLL)

Key points
- New therapies enable chemo-therapy free treatment & therapy of elderly and frail
- High-ranking publications e.g. NEJM, JCO, Lancet Oncology, Haematologica, JGO...
- Comorbidities (CIRS) are of prognostic relevance in CLL. Interactions of comorbidities and treatment?
- CLL-specific risk scoring based on GA does not exist yet. Relevance of GA in decision making?
- Scientific session on CLL tomorrow

RELEVANT PUBLICATIONS
  - New prognostic score Binet stage, ZAP-70 level, β2-microglobulin concentration and comorbidity (CIRS) identified two risk groups (low-risk: 0-1 parameters; high-risk: 2-4 parameters) with different overall survivals (median: 6.8 versus 11.4 years, P<0.001).
New targets and therapeutic agents in CLL

Shanafelt T., Hematology Am Soc Hematol Educ Program. 2013
ASH 2013 - New Orleans

- Presidential symposium
- Valentin Goede, Köln (German CLL Study Group)
- CLL 11 study
  - Inclusion
    - CIRS>6 and/or
    - Creatinine clearance >30 - <70ml/min

*Final publication: Goede V. et al., NEJM, 2014*
Goede V. et al., NEJM, 2014

**CLL11 Trial**

Clb + GA101 vs. Clb
- Median Age: 73 Years
- Median CIRS Score: 8

Stratified HR: 0.18
95% CI, 0.13-0.24
P<0.0001

**Progression-free survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>G-Clb</th>
<th>Clb</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>21</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>27</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>33</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>G-Clb</th>
<th>Clb</th>
</tr>
</thead>
<tbody>
<tr>
<td>238</td>
<td>220</td>
<td>218</td>
</tr>
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<td>207</td>
<td>188</td>
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<td>156</td>
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<tr>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Goede V. et al., NEJM, 2014*
Comorbidities negatively impact OS and PS and represent an independent prognostic parameter in multivariate analyses.

CLL was the major cause of death in patients with two or more comorbidities.

Durable control of CLL is critical to improve overall outcome of patients with increased comorbidity.

<table>
<thead>
<tr>
<th>No. of Comorbidities</th>
<th>0 or 1</th>
<th>≥ 2</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year mortality</td>
<td>25 %</td>
<td>40 %</td>
<td>2.1</td>
</tr>
<tr>
<td>Therapy-related</td>
<td>1 %</td>
<td>3 %</td>
<td>4.1</td>
</tr>
<tr>
<td>CLL-related</td>
<td>15 %</td>
<td>25 %</td>
<td>1.9</td>
</tr>
<tr>
<td>CLL-unrelated</td>
<td>4 %</td>
<td>8 %</td>
<td>2.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 %</td>
<td>4 %</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Goede et al., Haematologica 2014; epub ahead of print
Hematological malignancies - ALL

KEY POINTS

- Based on „pediatric like” strategies; elderly: 50+ yrs...
- Few data in elderly
- Sleeping beauty?

Relevant Publications

  - First retrospective evaluation of impact of comorbidities in elderly ALL; 89 patients 60+ yrs
  - Descriptive study; no impact of comorbidities on outcome
  - *We believe that comprehensive geriatric assessment should be performed and evaluated on a larger scale in elderly ALL*
AML - Relative survival by time and age based on SEER data

Klepin H D et al. JCO 2014;32:2541-2552
Hematological malignancies - AML

KEY POINTS
- Prognosis remains dismal for elderly
- Who is fit for intensive chemotherapy and/or HSCT?
- New drugs in clinical studies (demethylators, epigenetic modifiers, mAbs, inhibitors of cell cycle, aminopeptidase, Topoisomerase II, NF-κB, Aurora B kinase, nuclear export...)

RELEVANT PUBLICATIONS
- Klepin H et al. Blood 2013
  - Geriatric assessment predicts survival in AML; impaired cognition and PS is correlated with unfavourable OS
  - Individualizing treatment decisions for older adults with hematologic malignancies
- Elliot K. Leuk Res. 2014
  - Increased number of medications (≥4 versus ≤1) was associated with increased 30-day mortality, lower complete remission status, and higher overall mortality.
  - Polypharmacy warrants further study as a modifiable marker of vulnerability among older adults with AML.
**Hematological malignancies - MDS**

**KEY POINTS**

- Impact of comorbidities on clinical outcome is well established (>10 publications). Scores analysed included CCI, HCT-CI, MDS-CI, ACE-27.
- Who is fit for intensive chemotherapy and HSCT?
- Relevant clinical phase III studies have been finished; results will be presented at ASH
  - ESAs in anemic low-risk MDS (two studies)
  - Lenalidomid in anemic Non-5q- low-risk MDS
- Several promising drugs are applied in clinical studies

**RELEVANT PUBLICATIONS**

- Bammer C. et al., JGO 2014.
  - Comorbidities (based on HCT-CI) impact clinical outcome in elderly patients with MDS.
  - Distinct diseases cluster in an age- and sex-related manner.

*CCI, Charlson Comorbidity Index; HCT-CI, hematopoietic cell transplantation comorbidity index; MDS-CI, MDS-Specific Comorbidity Index; ACE-27, Adult Comorbidity Evaluation-27*
KEY POINTS

- Many activities
- Treatment algorithms based on geriatric assessment (CCI, ADL, iADL...)
- *Choice of therapy depends on potential side effects and preexisting comorbidities*
Hematological malignancies - Myeloma

The assessment of organ function, comorbidities (with the Charlson index), frailty, and disability (defined by ADL and IADL) should be considered to define patients' status (grade C/IV).

*Palumbo A. et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. JCO 2014.*
Hematological malignancies - Myeloma

Patients not eligible for autologous stem cell transplantation

Assessment of frailty

Go-Go
Regimens consisting of 2 or 3 drugs
Full dose

Moderate-Go
Regimens consisting of 2 (3) drugs
Reduced dose

Slow-Go
Regimens consisting of 1 or 2 drugs
Significant dose reduction

Options for initial treatment for at least 9 cycles

Bortezomib-based:
VMP, VD**, VCD**

Bortezomib-IMiD-based:
VMP-VT
VMPT-VT

IMiD-based:
Rd, conlRd
MPT
CTDa
MPR, CPR*

Other:
Bendamustine/Prednisone

+/- Maintenance

Ludwig H et al., The Oncologist 2014
Hematologic malignancies in elderly

How to promote and advance geriatric hematology?

- Cooperation hematologist/oncologist and geriatrician
- Cooperation with relevant societies
  - European School of Haematology (ESH) International Conference on Haematological Disorders in the Elderly. September 2013
  - European Hematology Association (EHA)
    - Theme of the year "Age and aging in blood disorders" (June 2013-June 2014)
    - Foundation of a Scientific Working Group «Aging and Hematology» (D. Bron)
      - First meeting and scientific session at EHA Congress 2014 in Milano
      - Second session planned for EHA Congress 2015 in Vienna
    - 2-days scientific meeting in Lisboa, May 1-3, 2015; Provisional scientific/organ. committee includes: D Bron, P Fenaux, T Fulop, V Goede, R Stauder
Hematologic malignancies in elderly

- American Society of Hematology (ASH)
  - Foundation of an “ASH hematology and aging committee” (H. Klepin); first meeting at ASH December 2014, New Orleans (involving C. Steer, R. Stauder from SIOG)
  - ASH 2014: Workshop on Hematology and Aging: *Highlighting Novel Science and Developing a Research Agenda*
    Planning committee Artz, Cohen, Klepin, Olin, Wildes

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Percentage of ASH-abstracts using the terms “older” and “elderly”, analysis performed by Klepin H.
ASH Annual Meeting Friday Scientific Workshop

Hematology and Aging: Highlighting Novel Science and Developing a Research Agenda

December 5, 2014
1:00-5:00PM
Moscone Center, South Building, Gateway Ballroom 104

Presented by the American Society of Hematology Aging Special Interest Group
Hematologic malignancies in elderly

KEY POINTS

- Integration in clinical studies (elderly are still under-represented)
- Definition of appropriate endpoints
  - Disease-specific survival (DSS): how many die of index-disease and how many of other causes?
  - PROs (patient reported outcomes)
- Integration of geriatric assessment
  - Nutritional status and cognition might be relevant
  - Relevance of objectively measured physical function; investigation of interventions to target physical vulnerability
  - Risk scoring, prediction of mortality, competing risks
  - Decision making, prediction of toxicity and therapy completion
  - New therapeutic compounds might overcome / mitigate the impact of some prognostic parameters
  - Tumor- and therapy-specific scoring systems should be developed
Update in Hematology
14th SIOG meeting
Lisboa, October 23rd, 2014

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