Relapsing APL

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French Belgian Swiss APL group

DES 1-2014
Frequency of relapse in APL?

In our ongoing APL 2006 trial:

• 350 standard risk patients aged <70 years included between Dec 2006 and Dec 2011
• 98% CR
• 7 relapses
Relapsing APL

• How do APL relapse?
• When should relapse be treated?
• Treatment of hematological relapse
• Treatment of extra hematological relapse
Relapsing APL

• How do APL relapse?
• When should relapse be treated?
• Treatment of hematological relapse
• Treatment of extra hematological relapse
How do APL relapse?

• Clinical relapse
  – Hematological
  – Extra hematological

• Molecular relapse
How do APL relapse?

- Clinical relapse
  - Hematological
  - Extra hematological
- Molecular relapse
Hematological relapses

• Generally during the first 3 years
• Late relapses :
  – Beyond 4 years: 12% of relapses (Kelaidi, Leukemia, 2007)
  – Nine (4.6%) relapses>3 years from CR, the last occurred after 4.6 years (Douer, Leuk Res, 2013)
Extra hematological relapses

- 1.5% (De Botton, 2006; Montesinos, 2009) to 3% (Vega-Ruiz, 2009) APL develop extramedullary relapse
- *Largely predominate in the CNS*
  - 10/14 (De Botton)
  - 7/8 (Vega-Ruiz)
- Often associated to molecular marrow relapse
Predictive factors of Extra hematological relapses

- De Botton (Leukemia, 2006):
  - age < 45
  - WBC >10 G/L
  - bcr 3

- Montesinos (Haematologica, 2009)
  - WBC >10G/L
  - CNS bleeding during induction

- Role of High dose AraC and/or intrathecal MTX+ AraC to prevent CNS relapse in patients with WBC > 10G/L? (De Botton, 2006; Lengfelder, 2008)
Outcome of extramedullary (EMD) relapse

- EMD carry a poor prognosis

- **Median survival from EMD relapse:**
  - 6.7 months (vs 26.3 for marrow relapses (De Botton, Leukemia, 2006)
  - 13 months (Montesinos, Haematologica, 2009)
  - 5 of 7 patients died within 4 months (Vega-Ruiz, Int J Hem, 2009)
How do APL relapse?

• Clinical relapse
  – Hematological
  – Extra hematological

• Molecular relapse
Molecular relapse

- Defined by 2 successive PCR positive assays, with stable or rising PML-RAR transcript levels detected in independent samples analyzed in 2 laboratories
- Evidence demonstrated with low sensitivity assays (10^-4)
- RQ-PCR can also capture most relapses at the molecular level (Grimwade, JCO, 2009)
- Justifies monitoring of mrd every 3 months?
Relapsing APL

• How do APL relapse?
• When should relapse be treated?
• Treatment of hematological relapse
• Treatment of extra hematological relapse
Should APL relapse be treated when only molecular?

Lo Coco (Blood, 1999)

- 14 molecular relapses
- Salvage treatment: ATRA+ CT +/- transplantation
- 12/14 molecular CR achieved
- 2 year outcome
  - Molecular relapse: 92% OS
  - Hematological relapse(historical): 44% OS
Should APL relapse be treated when only molecular?

_Esteve (Leukemia, 2007)_

- 52 relapses: 16 MOL, 36 HEM
- Salvage treatment: ATRA+ CT +/- transplantation
- 88 vs 81 % second molecular CR
- 5 year outcome
  - Hematological relapse: 64 % relapse, 24% OS
  - Molecular relapse: 30% relapse, 64% OS
Management of APL: recommendations from an expert panel on behalf of the European LeukemiaNet

Miguel A. Sanz,1 David Grimwade,2 Martin S. Tallman,3 Bob Lowenberg,4 Pierre Fenaux,5 Elihu H. Estey,6 Tomoki Naoe,7 Eva Lengfelder,8 Thomas Bu¨chner,9 Hartmut Do¨hner,10 Alan K. Burnett,11 and Francesco Lo-Coco BLOOD 2009

• Recommendation: For patients with confirmed molecular relapse (defined as 2 successive PCR-positive assays, with stable or rising PML-RARA transcript levels detected in independent samples analyzed in 2 laboratories) preemptive therapy has to be started promptly to prevent frank relapse.

• Level of evidence: IIa

• Grade of recommendation: B
Relapsing APL

• How do APL relapse?
• When should relapse be treated?
• Treatment of hematological relapse
• Treatment of extra hematological relapse
## Arsenic trioxide in relapsing APL

<table>
<thead>
<tr>
<th>Ref</th>
<th>Dosing</th>
<th>Nb pts</th>
<th>CR rate</th>
<th>Post induction</th>
<th>Long term outcome</th>
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<tbody>
<tr>
<td>Niu</td>
<td>0.15mg/kg/</td>
<td>47</td>
<td>85 %</td>
<td>As(_2)O(_3) alone (n =18)</td>
<td>12/18 relapses</td>
</tr>
<tr>
<td>Shen</td>
<td>0.08 mg/kg</td>
<td>20</td>
<td>80 %</td>
<td>As(_2)O(_3) + CT (n =11)</td>
<td>2/11 relapses</td>
</tr>
<tr>
<td>Kwong</td>
<td>10 mg</td>
<td>8</td>
<td>100 %</td>
<td>variable</td>
<td>2 year relapse free survival : 61 %</td>
</tr>
<tr>
<td>Soignet</td>
<td>0.15 mg/k</td>
<td>52</td>
<td>87 %</td>
<td>Allo or auto (n=12)</td>
<td>11 still in CR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>As(_2)O(_3) (n = 21)</td>
<td>9 still in CR</td>
</tr>
<tr>
<td>Ohnishi</td>
<td>0.15 mg/k</td>
<td>14</td>
<td>78 %</td>
<td>As(_2)O(_3)</td>
<td>median CR duration :</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 months</td>
</tr>
</tbody>
</table>
Treatment of APL molecular relapse by Gentuzumab ozogamycin (GO) (Lo Coco, Blood, 2004)

- 16 pts with molecular relapse (8, 5, 2, 1)
- GO 6mg/m2 x 2 + 1
- 14 molecular CR achieved
- 7 pts still in CR (7+ to 31+ months), 7 relapses after 3 to 15 months
GO in relapsed APL

- **Sustained molecular remission after low dose gemtuzumab-ozogamicin in elderly patients with advanced acute promyelocytic leukemia.** Breccia M, Haematologica. 2007

- **Gemtuzumab ozogamicin successfully induced molecular remission in relapsed therapy-related acute promyelocytic leukemia.** Shimokawa T, Rinsho Ketsueki. 2008

- **Sustained molecular remission after arsenic trioxide and gemtuzumab ozogamicin in a pediatric patient with relapsed acute promyelocytic leukemia.** Inoue A, Pediatr Hematol Oncol. 2012

- **Molecular remission induced by gemtuzumab ozogamicin in an elderly patient with relapsed acute promyelocytic leukemia.** Yago K, Rinsho Ketsueki. 2010

- **Treatment of relapsed acute promyelocytic leukemia with gemtuzumab ozogamicin and all-trans retinoic acid.** Tageja N, J Chemother. 2009
Other retinoids in relapsing APL?

Tamibarotene (Am 80)

- Differentiation (10 fold vs ATRA)
- Reduced affinity for CRABP

- Tobita (Blood, 1997): 24 relapses after ATRA. 58% CR
- Takeuchi (GTKR, 2006): 23 relapses. 78% CR
- **Naina HV** *(JCO, 2011)* Successful treatment of relapsed and refractory extramedullary APL with tamibarotene.
- Di Veroli (BJH. 2010) **Molecular remission in advanced APL after treatment with the oral synthetic retinoid Tamibarotene.**
Other retinoids in relapsing APL?

Liposomal ATRA (Tsimberidou, Leuk Lymphoma, 2006)

- 10 of 26 newly diagnosed APL treated with liposomal ATRA alone were still in CR at 5 years
• 4.2. Although ATRA in combination with chemotherapy can be used as salvage therapy, ATO-based regimens are presently regarded the first option for treatment of relapsed APL.

• IV

• C
Patients achieving second CR should receive intensification with SCT or chemotherapy, if possible.
Prognostic relevance of RT-PCR pretransplant in APL autografted in CR 2 (Meloni, Blood, 1997)

- 15 patients autografted in CR 2
- 7 PCR + in their pretransplant marrow: all relapsed after a median of 5 months
- 8 PCR-: 1 relapse, other patients in CR2 at a median of 26 months
## APL in CR2:Allo and auto SCT

(De Botton, JCO, 2005)

<table>
<thead>
<tr>
<th></th>
<th>Auto SCT</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>APL Study Group</strong></td>
<td><strong>APL Study Group</strong></td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td><strong>(Europe)</strong></td>
<td></td>
<td><strong>(Europe)</strong></td>
</tr>
<tr>
<td>No. Pts</td>
<td>50</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td><strong>21% (7 yrs.)</strong></td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td>79% (7 yrs.)</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td><strong>60% (7 yrs.)</strong></td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>TRM</td>
<td>6%</td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

Note: The table compares the outcomes of APL study groups for Allo and Auto SCT.
Event-free survival (EFS) from transplantation
Allo or auto in relapsing APL?

• Autologous and allogeneic SCT in APL in CR2 (Kohno, Int J Hemat, 2008)
  – 15 autos and 13 allos between 1999 and 2004
  – 4 year DFS 68.9% (auto) vs 46.2% (allo)

• Outcomes in patients with relapsed or refractory APL treated with or without auto or allo SCT. (Pemmaraju N, Clin Lymphoma Myeloma Leuk. 2013)
  – 7-year overall survival was 85.7%, 49.4%, and 40% in the auto-HCT, allo-HCT, and CT groups, respectively (P = .48).

• Autologous and allogeneic SCT in APL (Sanz, BMT, 2007)
  – 625 auto or allo after 1993
  – 5 year leukemia free survival
    • CR 2: 69% (auto)  68% (allo)
    • CR 1: 51% (auto)  59% (allo)
Allo SCT after ATO Salvage

Post-transplant survival (Soignet, Dombret, Sem Oncol, 2002)

Median follow-up: 30 months post SCT (range, 9.5 to 45)
Role of hematopoietic stem cell transplantation for relapsed acute promyelocytic leukemia: A retrospective analysis of JALSG-APL97

Hiroaki Fujita, 1,2,3 Moto Asou, 4,5 Masako Ishanaka, 6 Rei His, 1 Shosaku Nomura, 7 Hitoshi Kiyoi, 7,8 Masaya Okada, 7 Yoou Infaguma, 7,9 Mitsuro Matsuda, 9,10 Takashi Yamada, 10,11 Shigeki Ohtake, 10,11 Tohru Iizumi, 12,13 Chiaki Nakaseko, 12,13 Yoshiki Ishigatsubo, 12,13 Kanshi Shinagawa, 14 Akito Takashita, 14 Yasushi Miyazaki, 14 Kazunori Ohnishi, 14 Shuichi Miyawaki, 14 Tomoaki Nace 15 and for the Japan Adult Leukemia Study Group

Acute Myeloid Leukemia

Allogeneic stem cell transplantation for advanced acute promyelocytic leukemia in the ATRA and ATO era

Safaa M. Ramadan, 1,2 Ambra Di Veroli, 3 Agnese Camboni, 1 Massimo Breccia, 1 Anna Paola Iori, 1 Franco Aversa, 1 Luca Cupolillo, 1 Cristina Papayannidis, 1 Andrea Bacigalupo, 1 William Arcese, 1 and Francesco Lo-Coco 1,2

B

PCR status at SCT

Overall survival probability (%)

0 10 20 30 40 50 60 70 80 90 100

0 6 12 18 24 30 36 42 48

PCR-ve PCR+ve

Months from SCT

AT RISK

PCR-ve 15 13 10 10 8 7 7 7 5

PCR +ve 16 9 5 4 4 4 4 4 4

5-year OS:

Auto-HSCT: 63.3%

Allo-HSCT: 76.2%
Non-HSCT: 75.3%

5-year EFS:

Auto-HSCT: 41.7%

Allo-HSCT: 71.1%
Non-HSCT: 45.4%

5-year CIR:

Auto-HSCT: 58.3%

Allo-HSCT: 9.8%
Non-HSCT: 51.0%
Phase 2 study of arsenic trioxide followed by autologous hematopoietic cell transplantation for relapsed acute promyelocytic leukemia

Masamitsu Yanada, Motohiro Tsuzuki, Hiroyuki Fujita, Katsumichi Fujimaki, Shin Fujisawa, Kazutaka Sunami, Masafumi Taniwaki, Akira Ohwada, Kosuke Tsuboi, Akio Maeda, Akihiro Takeshita, Shigeki Ohtake, Yasushi Miyazaki, Yoshiko Aitsuta, Yukio Kobayashi, Tomoki Naoe and Nobuhiko Emi
Nine patients with relapsed APL treated with prolonged ATRA and ATO

All patients received ATO/ATRA according to the schedule reported by Estey et al

Of the 9 patients, 8 remained in prolonged second CRm for a median time of 25 months (range 11-50)
Management of APL: recommendations from an expert panel on behalf of the European LeukemiaNet

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• 4.4. Allogeneic HSCT is recommended for patients failing to achieve a second molecular remission.

• IV

• C
• 4.5. Autologous HSCT is a valid option for patients without detectable MRD in the marrow and with an adequate PCR negative harvest.

• IIa

• B
4.6. For patients in whom HSCT is not feasible, the available options include repeated cycles of ATO with or without ATRA with or without chemotherapy.

- IV
- C
As203 in relapsing APL: French Belgian Swiss experience
(X Thomas et al, Hematologica, 2006)

- 28 pts (R1=22;R>1=6) between 2002 and 2005
- Median previous CR duration 20 m (1-74)
- 24 CR, 2 early deaths, 2 leukemic resistance
### As2O3 in relapsing APL: French Belgian Swiss experience

(X Thomas et al)

<table>
<thead>
<tr>
<th></th>
<th>With As2O3</th>
<th>Without As2O3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y LFS</td>
<td>84%</td>
<td>47%</td>
</tr>
<tr>
<td>2 y OS</td>
<td>79%</td>
<td>51%</td>
</tr>
<tr>
<td>Grade III-IV infections</td>
<td>24%</td>
<td>54%</td>
</tr>
</tbody>
</table>
Relapsing APL

• How do APL relapse?
• When should relapse be treated?
• Treatment of hematological relapse
• Treatment of extra hematological relapse
For patients with CNS relapse, induction treatment consists of weekly triple intrathecal therapy (ITT) with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the cerebrospinal fluid, followed by 6 to 10 more spaced out ITT treatments as consolidation. Systemic treatment should also be given.
New treatments in extramedullary (EMD) relapse

- **ATO Au** (Blood, 2009): cerebrospinal fluid arsenic linearly correlated to plasma arsenic level (17.7%), with individual variations
  - Plasma/CSF ratio not influenced by intrathecal chemotherapy or blasts in CSF
  - Therapeutic levels obtained in CSF in all patients tested

- **intrathecal liposomal Ara C**

- 6 first relapses involving the CNS, representing 3% of the relapses

- pts salvaged by intrathecal CT, combined to ATRA and systemic CT in APL 93, and ATO in APL 2000 trial.

- 4 pts durably salvaged by auto SCT (n= 3 ) and 1 after ATO and CT
Perspectives in relapsing/refractory APL

- Very few truly resistant cases (< 0.5%)
- Fewer relapses…but more difficult to treat
- Mechanisms of relapse/resistance?
  - PML- RAR gene mutations
    - RAR (Gallagher, Blood, 2102)
    - PML (Goto, Blood, 2011)
  - Other mechanisms?
    - Whole genome sequencing
Treatment of APL in specific subgroups

- Older patients
- Children
Treatment of newly diagnosed APL in the elderly (Ades, ASH 2009)

• Joint analysis of elderly patients included in:
  – PETHEMA group trials (LPA96 and LPA99)
  – European APL group trials (APL93 and APL2000).

• 1575 consecutive newly diagnosed APL pts enrolled in the 4 trials,
  – 1288 (81%), aged <60 y
  – 105 (6.6%), aged 60-65 y
  – 91 (5.7%) aged 65-70 y
  – 91 (5.7%) and aged > 70 y
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age = &lt;60</th>
<th>Age = 60-65</th>
<th>Age = 65-70</th>
<th>Age &gt;=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39</td>
<td>62</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>WBC</td>
<td>3.1</td>
<td>4.58</td>
<td>2.56</td>
<td>1.6</td>
</tr>
<tr>
<td>Platelets</td>
<td>24</td>
<td>23</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.53</td>
<td>1.5</td>
<td>1.7</td>
<td>1.78</td>
</tr>
<tr>
<td>Sanz’s Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>19.7%</td>
<td>27.6%</td>
<td>29.6%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Int</td>
<td>51.9%</td>
<td>37.4%</td>
<td>39.6%</td>
<td>46.1%</td>
</tr>
<tr>
<td>High</td>
<td>28.3%</td>
<td>35.2%</td>
<td>30.7%</td>
<td>25.3%</td>
</tr>
</tbody>
</table>
Complete Remission (CR) Rate

- CR rate was significantly higher in younger patients
- And decreased with age (p=0.002)
- Only reason for decreased CR rate in elderly patients: more early deaths

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;60 y</th>
<th>60-65 y</th>
<th>65-70 y</th>
<th>&gt;70 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR Rate (%)</td>
<td>94.6%</td>
<td>84.8%</td>
<td>81.8%</td>
<td>78.4%</td>
</tr>
</tbody>
</table>
Cumulative incidence of Relapse (CIR)

- 5y-CIR similar in young and elderly patients (p=0.63)
- Death in CR increased with age

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;60 y</th>
<th>60-65 y</th>
<th>65-70 y</th>
<th>&gt;70 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>5y CIR (%)</td>
<td>16.5%</td>
<td>19.1%</td>
<td>11.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Death in CR</td>
<td>3.1%</td>
<td>11.8%</td>
<td>14.6%</td>
<td>17.8%</td>
</tr>
</tbody>
</table>
Overall Survival curve

Overall Survival (%)

Less than 60 y
60-65 y
65-70 y
>70 y

Time (Months)
All-trans retinoic acid and anthracycline monochemothotherapy for the treatment of elderly patients with acute promyelocytic leukemia

Miguel A. Sanz, Edo Vellenga, Chelo Rayón, Joaquín Díaz-Medialdea, Concha Rivas, Elena Amutio, Jesús Arias, Guillermo Deben, Andrés Novo, Juan Bergua, Javier de la Serna, Javier Bueno, Silvia Negri, José M. Beltrán de Heredia and Guillermo Martín
APL in children
(Bally, JCO, 2012)

- **Protocol**
  - APL93: 576 patients, 69%
  - APL2000: 257 patients, 31%

- **Age**
  - 0-12y: 26 patients, 3%
  - 13-18y: 58 patients, 7%
  - 19-65y: 749 patients, 90%
### Pt characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;12</th>
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<th>Age = 19-65</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>6</td>
<td>16.5</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td><strong>WBC (G/L)</strong></td>
<td>10.8</td>
<td>2.6</td>
<td>2.7</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Platelets(G/L)</strong></td>
<td>23</td>
<td>23</td>
<td>32</td>
<td>0.02</td>
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<tr>
<td><strong>Fibrinogen (g/l)</strong></td>
<td>1.4</td>
<td>1.4</td>
<td>1.6</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Sanz’s Score</strong></td>
<td>3 (12%)</td>
<td>15 (26%)</td>
<td>336 (34%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10 (38%)</td>
<td>27 (47%)</td>
<td>415 (42%)</td>
<td></td>
</tr>
<tr>
<td>Int</td>
<td>13 (50%)</td>
<td>16 (28%)</td>
<td>244 (24%)</td>
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</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>%M3v</strong></td>
<td>23</td>
<td>24</td>
<td>13</td>
<td>0.03</td>
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</table>
Complete Remission Rate

- Complete Remission rate was similar across all age groups

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;12 y</th>
<th>13-18y</th>
<th>19-65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR Rate (%)</td>
<td>92%</td>
<td>100%</td>
<td>94.5%</td>
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</table>
Cumulative incidence of Relapse

- The 5 year cumulative incidence of relapse (CIR) was rather similar across age groups

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;12 y</th>
<th>13-18y</th>
<th>19-65 y</th>
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</thead>
<tbody>
<tr>
<td>5y-CIR (%)</td>
<td>33%</td>
<td>20%</td>
<td>23%</td>
</tr>
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</table>

p=0.3

p=0.5
## Children

<table>
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<tr>
<th>Age (y)</th>
<th>0-4 years</th>
<th>5-12 years</th>
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<tbody>
<tr>
<td>WBC (G/L)</td>
<td>8</td>
<td>14,8</td>
</tr>
<tr>
<td>Platelets (G/L)</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>1,75</td>
<td>1,4</td>
</tr>
<tr>
<td>Sanz’s Score</td>
<td>Low 3 (12%)</td>
<td>10 (38%)</td>
</tr>
<tr>
<td></td>
<td>Int 13 (50%)</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>%M3v</td>
<td>23</td>
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# Outcome of children <4 years

<table>
<thead>
<tr>
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<th>5-12 years</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>CR rate</strong></td>
<td>11/12</td>
<td>13/14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>5 year Cumulative incidence of relapse</strong></td>
<td>47%</td>
<td>18.9</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>5 year Overall Survival</strong></td>
<td>72%</td>
<td>78.9</td>
<td>NS</td>
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</tbody>
</table>
Very young children

Aged 0-12 y

Aged 0-4 y

Aged 5-12 y
European Project
for Salvage Therapy of Relapsed APL

Treatment Recommendation
Registry

10th Annual Symposium of the European LeukemiaNet
5th February 2013

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Patients with Relapsed APL treated with ATO in 1st Relapse (132 of 223 registered Pts)

- 20/29 - UK
- 30/56 - France
- 42/48 - Spain
- 10/15 - Germany
- 23/60 – Italy
- 6/8 - Greece
- 1/6 - Scandinavia
- 0/1 - Poland
Available therapeutic options

1. Intensification therapy
   a. AutoSCT
   b. AlloSCT
   c. ATRA + HD/CHT ± AutoSCT

2. Maintenance therapy
   a. ATRA + LD/CHT
   b. ATRA + ATO ± GO

Criteria for choice

1. PCR status: AutoSCT can be considered only in PCR -ve cases
2. Donor availability
3. Age, clinical condition, and other considerations, at centre discretion, can determine the option of either intensification or maintenance therapy.

European Recommendation for Salvage Therapy in Relapsed APL with ATO

Induction
ATO
Consolidation
ATO + ATRA
Molecular assessment (RT-PCR)
## Registered Patients with Relapsed APL (26th of Jan., 2013)

<table>
<thead>
<tr>
<th>Therapy with ATO in first relapse</th>
<th>n = 132</th>
</tr>
</thead>
<tbody>
<tr>
<td>hematological</td>
<td>n = 84 (bone marrow)</td>
</tr>
<tr>
<td>molecular</td>
<td>n = 38 (bone marrow)</td>
</tr>
<tr>
<td>extramedullary</td>
<td>n = 10 (CNS 8, other 2)</td>
</tr>
</tbody>
</table>
ATO: 0.15 mg/m²/day (or comparable regimens)
ATRA: 45 mg/m²/day

**Induction therapy (n=132):** median duration: 34 d (16 - 93)
- ATO mono: 67%
- ATO + ATRA: 34%

**First consol. cycle (n=100):** 5 days weekly for 5 weeks
- ATO mono: 50%
- ATO + ATRA: 35%
- other: 15%

**Intrathecal therapy:** methotrexate ± ara-C ±
hydrocortisone

CNS relapse: ± irradiation±chemotherapy
(prophylaxis, few cases)
### Treatment Results (n=126)

<table>
<thead>
<tr>
<th></th>
<th>Molecular relapse (n=37)</th>
<th>Hematological relapse (n=79)</th>
<th>Extramedullary relapse (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results after induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (hematological)</td>
<td>70/79 88%</td>
<td>6/79 8%</td>
<td>6/7 86%</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>6/79 8%</td>
<td>0</td>
</tr>
<tr>
<td>Resistance</td>
<td>3/79 4%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PCR -ve</td>
<td>19/36 53%</td>
<td>30/62 48%</td>
<td>9/9 100%</td>
</tr>
<tr>
<td>PCR +ve)</td>
<td>17/36 47%</td>
<td>32/62 52%</td>
<td>0</td>
</tr>
<tr>
<td>Results after consolidation 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular remission</td>
<td>16/25 64%</td>
<td>29/42 69%</td>
<td>6/7 86%</td>
</tr>
</tbody>
</table>
# Symptoms/ Side Effects during Induction Therapy with ATO

<table>
<thead>
<tr>
<th>Symptoms during induction with ATO (evaluable patients)</th>
<th>Mol. + extramed. relapse</th>
<th>Hematolog. relapse</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APL diff. Syndrome (n=111)</td>
<td>2 %</td>
<td>19 %</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dexamethason (n=110)</td>
<td>2 %</td>
<td>25 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocytosis/ chemoth. (n=122)</td>
<td>0</td>
<td>35 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interruption of ATO (n=113)</td>
<td>2 %</td>
<td>18 %</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Overall Survival after First Relapse

n = 126

Median follow up 2.7 y (5 d – 9.5 y)

57.4%
Event Free Survival after First Relapse

\[ n = 126 \]

Percent Event Free Survival

Years from First Relapse

total: \( N = 126 \) (Censored 90)
Postconsolidation Therapy (n=126)

<table>
<thead>
<tr>
<th>Patients</th>
<th>RT-PCR at transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Allo. transpl.</td>
<td>23</td>
</tr>
<tr>
<td>Auto. transpl.</td>
<td>46</td>
</tr>
<tr>
<td>No transpl.</td>
<td>57</td>
</tr>
</tbody>
</table>

(further ATO ± GO, chemotherapy, too early)
Overall Survival according to Postconsolidation Therapy

( allo Tx : 67.6 %. auto Tx : 58.2 %. no trans : 59 Mon., 46 %. p = 0.04549 )