A WT-1 and PRAME “Fast-DC” Immunotherapy as a Potential post-Remission Strategy for AML

Yngvar Floisand, MD, PhD

Co-authors: Iris Bigalke, MD, Dag Josefsen, MD, PhD, Silke Raffegerst, PhD, Frauke Schnorfeil, PhD, Richard Addo, MD, PhD, Dolores J. Schendel, PhD, Kai Pinkernell, MD, Gunnar Kvalheim, MD, PhD

1) Department of Hematology, Oslo University Hospital, Oslo, Norway,
2) Department of Cellular Therapy, Oslo University Hospital, Oslo, Norway,
3) Medigene Immunotherapies GmbH, Munich, Germany

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Introduction

- The medical need for patients with AML, not eligible for allogeneic HSCT, remains high.

- Vaccination against leukemia-associated antigens could provide a possibility for disease control.

- A post-remission vaccination strategy was carried out in a Phase I/II clinical trial against the antigens:
  - WT-1, a leukemia-associated antigen
  - PRAME, a cancer-testis antigen
Study overview

- Single center, open-label Phase I/II trial (ClinicalTrials.gov Identifier: NCT02405338)

- Key inclusion criteria:
  - AML in CR or CR<sub>i</sub> after induction/consolidation chemotherapy
  - Not eligible for allogeneic hematopoietic stem cell transplantation
  - Expression of antigen WT-1 with or without the antigen PRAME

- Continuous vaccination for 2 years or until progression/death

- Primary objectives
  - Safety and feasibility

- Secondary objectives (among others):
  - Overall survival (OS)
  - Progression free survival (PFS)

Vaccination schedule:
Personalized cancer treatment using a mature DC vaccine

1. Isolation of DC precursor cells from patient’s blood
2. GMP: generation of mDCs and loading of DCs with tumor-target antigens using ivt-RNA
3. GMP: freezing of vaccine cells in multiple aliquots and release testing (DC vaccine product)
4. Thawing and application to patient (vaccination)

- Patients received 2.5 or 5.0 million mature DCs per antigen (WT-1 or PRAME) per vaccination
- DC vaccines were applied by intradermal injection (200 µl per antigen)
Baseline demographics and parameters

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<table>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>20</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female:</td>
<td>5</td>
</tr>
<tr>
<td>Male:</td>
<td>15</td>
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<tr>
<td>Median age</td>
<td>59 years (Range 24-73)</td>
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<tr>
<td>ECOG</td>
<td>0 (100%)</td>
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<td>Prognostic Risk classification (HOVON/SAKK 102)</td>
<td>Poor: 2  Intermediate: 5  Good: 13</td>
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<td>Mean time from diagnosis to first vaccination (±StDev)</td>
<td>10.1 ± 3.7 months (Range 4.5-17.5)</td>
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<td>Mean time from last chemotherapy of last regimen to first vaccination (±StDev)</td>
<td>7.2 ± 3.4 months</td>
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Safety and tolerability of DC vaccines

- No vaccine related SAE or SUSAR was reported
- No patient was withdrawn due to toxicity or intolerability
- Grade I/II toxicity was experienced by 18 (90%) of the 20 patients
  - Most common AEs were grade I injection site related, accounting for 28% (22 out of 80) of all AEs
- Grade III toxicity was experienced by (25%) patients and all unrelated to the vaccine:
  - 3 patients with thrombocytopenia grade III due to an imminent relapse
  - 2 other grade III AEs (1 upper respiratory tract infection; 1 herpes zoster)
Feasibility of DC vaccine production

- DC vaccines could be produced for all 20 patients included in the clinical trial
- 17 out of 24 DC productions yielded 20 or more vaccine doses
- 5 patients needed apheresis twice for vaccine production, the remaining patients received all vaccines produced from one apheresis.
Overall survival (OS) rate

- The 2-year OS rate was estimated at 80% (95% CI: 55-92%)
- 80% OS rate was identical in patients < 60 years as well as ≥ 60 years (10 patients per age group)

Overall survival from first IMP vaccination, Kaplan-Meier curve
Progression free survival (PFS) rate

- The 2-year PFS rate was estimated at 55% (95%CI:31-74%)
- A total of 9 patients progressed, 5 of which were within 80 days after 1st vaccination
- 2-year PFS rate:
  - patients < 60 years 60% (95%CI:25-83%)
  - patients ≥ 60 years 50% (95%CI:18-75%)

Kaplan-Meier curve, Progression free survival from first IMP vaccination
Among the 9 progressing patients:
- 6 could undergo allogeneic HSCT
- Allogeneic HSCT was performed 104-380 days after first vaccination
- Risk categories: 4 good, 2 poor risk
Disease course after progression

Among the 9 progressing patients:
- 4 patients in total died (including 2 of the transplanted patients)
  - 3 patients died to the underlying disease
  - 1 patient died due to GvHD after aHSCT

![Pie chart showing disease course]

- 5 patients in remission
- 2 patients in relapse
- 2 patients dead
- 2 patients underwent aHSCT
- 2 patients underwent Chemo

- 6 patients < 60 years old
- 6 patients ≥ 60 years old

The pie chart visually represents the distribution of patients across different statuses and age groups.
Mutational load in relation to relapse

- 23 common mutations were analysed: ASXL1, BCOR, CALR, CBL, CEBPA, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF1

- As expected, higher mutational load correlated with relapse
Activation of T-cells in the bone marrow

- The number of activated, HLA-DR+/CD3+ T cells is increased in bone marrow and peripheral blood (not shown) of patients that stay in remission.

![Graph showing the percentage of HLA-DR+ T cells in bone marrow between relapsing patients and patients in remission. The graph displays individual patient data points with error bars indicating variability.]
Summary

- A fast DC immunotherapy against WT-1 and PRAME in post-remission AML patients is safe and well tolerated, which is particularly important for elderly patients.
- The vaccines could be manufactured in all patients, despite chemotherapy pretreatment.
- PFS and OS showed encouraging results at 2 years in this first in human clinical trial in 20 patients.
- Specifically, the OS in patients ≥ 60 years of 80% at 2 years is worth highlighting and warrants further studies to assess efficacy.