Targets for the treatment of drug resistant chronic lymphocytic leukemia

Tonino, S.H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
R-DHAP is effective in fludarabine-refractory chronic lymphocytic leukemia

Sanne H. Tonino
Michel van Gelder
Eric Eldering
Marinus H. van Oers
Arnon P. Kater

Leukemia 2010 Mar;24(3):652-4
Fludarabine-refractory chronic lymphocytic leukemia (CLL) infers a very poor prognosis, with a median life expectancy of less than one year \(^1\). Although alemtuzumab, the only registered drug for the treatment of fludarabine refractory CLL, is effective in this patient category, its use is hampered by an increased risk of major opportunistic infections. Also, effectivity is rather low in patients with bulky disease \(^1\). The only means by which enduring remissions in patients with refractory CLL can be achieved is reduced intensity allogeneic hematopoietic stem cell transplantation (RIST). Response to induction treatment prior to RIST is found to be an important determinant of long-term outcome as patients with high disease burden, particularly bulky lymphadenopathy at time of transplantation or poor response to last treatment, have the tendency to relapse more often, whereas patients with progressive disease uniformly do bad \(^2\). Currently, no optimal induction regimen, especially for patients with chemorefractory disease, has been established.

In relapsed B cell non-Hodgkin lymphoma the DHAP-regimen (dexamethasone, cytarabine and cisplatin) has been used as an effective salvage treatment and also as induction therapy prior to (autologous) stem cell transplantation. Moreover, a recent study showed improved efficacy of the addition of the anti-CD20 monoclonal antibody rituximab to a DHAP-based induction regimen \(^3\). Although platinum-based therapies are presently not often used in CLL, these data provide an incentive to investigate its efficacy in relapsed and refractory CLL.

A 36-year old male patient (patient 1) was referred to our clinic with progressive CLL, Rai stadium III with adverse prognostic characteristics (CD38 positivity, unmutated IgV\(_H\)-genes), and bulky lymphadenopathy. As shown in table 1, he had been treated extensively over a period of 1.5 years without response. At time of referral the patient had fludarabine-refractory disease according to the NCI criteria and cytogenetic analysis showed deletion of 17p (FISH probe p53 (Abbott-Vysis)) in 87% of the CLL cells. R-DHAP (dexamethasone 40 mg days 1-4, cisplatin 100mg/m\(^2\) day 1, cytarabine 2 x 2g/m\(^2\) day 2 and rituximab 375 mg/m\(^2\) day 5, every three weeks) was chosen as induction regimen and a donor search for allogeneic stem cell transplantation was initiated. Already within a few weeks after the first cycle of therapy, the peripheral blood lymphocyte count decreased more than 20-fold from 78 x 10\(^9\)/L to 3.3 x 10\(^9\)/L.

To further study the efficacy of this regimen, we next retrospectively analyzed 9 additional CLL patients with chemorefractory disease treated with R-DHAP. Patient characteristics are presented in Table 1. The mean age of the patients was 54 years. One patient had a WHO performance status (PS) of 2; otherwise the PS was 0-1 at time of the first cycle of R-DHAP. Seven patients had high-risk disease based on the Rai-classification and 8 had bulky lymphadenopathy, defined as lymphadenopathy > 5cm. Cytogenetic abnormalities, including 2 cases of 17p deletion and 2 cases of 11q deletion, were found in 4 patients. All patients had undergone multiple preceding therapies as indicated. Nine patients had previously been treated with fludarabine; 6 of whom suffered from relapse within 6 months and the remaining 3 within 1 year.
A total of 1 to 4 cycles of R-DHAP was administered. Eight of the 10 patients responded (80%); a partial remission, as defined by the revised iwCLL-criteria, was obtained in 7 out of 10 patients and a complete response in 1 patient. In this patient the absence of minimal residual disease (MRD) was confirmed by four-color flowcytometry. One of the two patients with del17p and both patients with del11q responded. Interestingly, a significant decrease in lymphadenopathy was attained in 6 of 8 patients with bulky disease. One patient developed tumour-lysis syndrome after the first cycle of R-DHAP, for which one dose of rasburicase was administered. All patients experienced grade III or IV hematological toxicity, although treatment effects could not always be discriminated from disease related cytopenias. No life-threatening events occurred. Three patients developed infectious complications, requiring in-hospital antibiotic treatment (grade III). Six patients (nos 3, 5-7, 9 and 10) subsequently underwent RIST; there was no appropriate donor available for patient 2 (Sib or MUD), whereas patient 1, 4 and 8 were considered not eligible for stem cell transplantation. Follow-up after the last cycle of R-DHAP is too short do draw firm conclusions as the end-points of progression-free survival and overall survival are not yet reached in 5 patients. However, progression-free survival and overall survival extended beyond the median follow-up of 12 months in 3 and 4 patients respectively.

Knowledge about mechanisms by which drug-resistance is overcome by this regimen and which constituents of the regimen are important in this process, will provide valuable information for further research into treatment modalities for chemorefractory CLL.

<table>
<thead>
<tr>
<th>Pt no</th>
<th>Gender and Age</th>
<th>PS¹</th>
<th>FISH²</th>
<th>Rai</th>
<th>Bulky disease³</th>
<th>Preceding therapies⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M 36</td>
<td>1</td>
<td>del 17p</td>
<td>IV</td>
<td>+</td>
<td>CA, CVP, FCR, Alem, R-CHOP</td>
</tr>
<tr>
<td>2</td>
<td>M 65</td>
<td>1</td>
<td>Normal</td>
<td>II</td>
<td>-</td>
<td>CA, CVP, F</td>
</tr>
<tr>
<td>3</td>
<td>M 71</td>
<td>1</td>
<td>Normal</td>
<td>IV</td>
<td>+</td>
<td>CA, F, FC, FCR</td>
</tr>
<tr>
<td>4</td>
<td>M 51</td>
<td>2</td>
<td>Normal</td>
<td>II</td>
<td>+</td>
<td>CA, F, FCR</td>
</tr>
<tr>
<td>5</td>
<td>F 47</td>
<td>0</td>
<td>del 11q</td>
<td>IV</td>
<td>+</td>
<td>FCA, Alem</td>
</tr>
<tr>
<td>6</td>
<td>F 53</td>
<td>0</td>
<td>ND</td>
<td>III</td>
<td>-</td>
<td>CA, F, Alem</td>
</tr>
<tr>
<td>7</td>
<td>F 54</td>
<td>0</td>
<td>ND</td>
<td>III</td>
<td>+</td>
<td>CA, F, FCR, R-CHOP</td>
</tr>
<tr>
<td>8</td>
<td>M 65</td>
<td>1</td>
<td>ND</td>
<td>IV</td>
<td>+</td>
<td>CA, CVP, F, CHOP, Alem</td>
</tr>
<tr>
<td>9</td>
<td>M 57</td>
<td>1</td>
<td>del 17p</td>
<td>II</td>
<td>+</td>
<td>R-CVP, R-CHOP</td>
</tr>
<tr>
<td>10</td>
<td>M 50</td>
<td>1</td>
<td>del 11q</td>
<td>IV</td>
<td>+</td>
<td>Chl, FCR, Alem</td>
</tr>
</tbody>
</table>

¹ Performance status according to WHO-criteria. ² FISH = fluorescence in situ hybridization for cytogenetic changes: del 17p, del 11q, trisomy 12, del 13q; ND = not performed. ³ Bulky disease is defined as lymphadenopathy > 5 cm at at least one location. ⁴ CA = chlorambucil, CVP = cyclophosphamide/vincristine/prednisone, F = fludarabine, FC(R)(A) = fludarabine/ cyclophosphamide/ (rituximab)(ofatumumab), Alem = alemtuzumab, CHOP = cyclophosphamide/ doxorubicin/ vincristine/ prednisone. ⁵ Fludarabine resistance according to NCI-criteria (1996, revised in 2008; relapse within 6 months of fludarabine containing regimen); NA = not applicable.
We studied in vitro sensitivity to fludarabine on serial blood samples taken from patient 1 before and 24 and 48 hours after start of treatment (before administration of cytarabine) and found that in vitro fludarabine resistance was abolished following 48 hours of in vivo treatment (Figure 1A). Since both cisplatin and dexamethasone are administered during the first 48 hours of the R-DHAP regimen, we attempted to dissect the contribution of these drugs to the observed synergy with fludarabine (F-ara-A) in both p53 functional (n=3) and dysfunctional (n=3) CLL samples. As expected, p53 functional CLL cells were sensitive to 10 μM fludarabine (F-ara-A), whereas p53 dysfunctional CLL samples were not. Co-treatment with 10 μM dexamethasone, but especially 10 μM cisplatin (CDDP), resulted in a synergistic response, importantly also in p53 dysfunctional samples (Figure 1B). Although these in vitro data are preliminary, this observation needs to be investigated further as it may offer insight into new possibilities to overcome p53 dysfunction in drug responses in CLL.

In our retrospective analysis, we found marked effectivity of the R-DHAP regimen in chemorefractory CLL, of note also in patients with bulky lymphadenopathy. Synergistic interactions between nucleoside analogs and oxaliplatin have been described in early stage, previously untreated CLL samples 4, but our data suggest that also in patients with fludarabine resistance sensitivity to this drug can be enhanced by platinum-based compounds.

However, before the R-DHAP regimen can be generally considered as a treatment option in high-risk CLL patients, the results of a current prospective Dutch/Belgian HOVON trial studying the efficacy and tolerability of this regimen prior to allo-SCT in CLL patients would be needed.
with fludarabine–resistant disease, should be awaited. Our findings are in line with a previous small study, in which 2 courses of DHAP followed by alemtuzumab were used as conditioning regimen prior to autologous transplantation in chemorefractory CLL}. In addition, a phase I-II trial in which a comparable regimen (OFAR; consisting of oxaliplatin, fludarabine, cytarabine and rituximab) was used, yielded moderate though encouraging results in chemorefractory patients; 33% of patients with fludarabine-resistant CLL (and 37% of patients with documented deletion of 17p) responded. Together these results provide a rationale to explore the efficacy and mechanism of action platinum-based regimens in this patient category. A drawback of regimens containing platinum-based compounds is the rather substantial risk of hematological toxicity, especially in patients with already compromised hematopoiesis due to the disease. Therefore the potential benefit of alternative regimens like the combination of high dose methylprednisolone and rituximab, which showed considerable effectivity (an overall response rate of 93%) in a small study in a similar patient group, and the newer targeted compounds (reviewed by Tsimberidou), should be explored unabatedly.

Acknowledgements

The authors would like to thank GA Huls, MD PhD (University Medical Center, Groningen), S Hovenga, MD PhD (Nij Smellinghe Hospital, Drachten) and SH Wittebol, MD (Meander Medical Center, Amersfoort) for providing patient data.

Figure 1. R-DHAP sensitizes chemorefractory CLL to fludarabine. (A) Samples taken before and after 24 and 48 hours of in vivo treatment, were treated with 10 μM fludarabine (F-ara-A) for 48 hours. Presented is % cell death upon F-ara-A treatment corrected for baseline apoptosis of the sample (mean ± SEM of 4 tests; Mann-Whitney-U test). (B) P53 dysfunctional (p53–; n=3) and p53 functional (p53+; n=3) CLL samples were treated with 10 μM cisplatin (CDDP) or 10 μM dexamethasone (dexa) combined with 10 μM F-ara-A. To assess synergy, drug interactions were analyzed as described by Kaspers et al. In short, actual survival (as assessed by MitoTracker staining) is plotted against expected survival, calculated from the survival rates of samples treated with the individual drugs. The diagonal line represents the situation in which actual survival = predicted survival. Dots beneath this line indicate synergistic drug interactions (as actual survival < predicted survival).
Reference List


