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Manuscript Draft

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Title: Treatment of 5q- Syndrome with Lenalidomide in an HIV-positive Patient under cART

Article Type: Letter to the Editor

Keywords: 5q-Syndrome, MDS, HIV, Lenalidomid

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Abstract: We report on a 52 year old HIV+ patient with an undetectable viral load for the past 10 years on combined antiretroviral therapy (cART) who developed 5q-syndrome and was successfully treated with lenalidomide. After 2 cycles, complete normalisation of peripheral blood counts was achieved and phlebotomy therapy was started for iron overload. After 5 cycles, BM examination revealed complete cytological and partial cytogenetic remission (5q deletion in 8 of 50 metaphases). HIV viral load remained undetectable before, 1, 2, 3, 4, 8, 12 and 24 weeks after the start of lenalidomide. CD4+ cells had reached a steady state between 137 and 206 cells/mm³ previous to lenalidomide. They rose to 235 cells/mm³ 2 months after lenalidomide start and remained stable between 230 and 240 cells/mm³.

Before lenalidomide treatment, plasma concentrations of atazanavir (ATV) and lopinavir (LPV) were 1767 ng/ml and 13903 ng/ml 5 hours after last drug intake. On day 23 and 28 of cycle 2 of lenalidomide treatment, plasma levels 11.5 hours after last drug intake were 2728 ng/ml and 2180 ng/ml for ATV, and 7728 ng/ml and 5791 ng/ml for LPV, respectively. At day 20 of cycle 3, ATV and LPV plasma concentrations were 2370 ng/ml and 8378 ng/ml, 11.75 hours after last drug intake. This is the first report on lenalidomide administration to an HIV+ patient with 5q-syndrome without interruption of cART. Plasma levels of ATV under lenalidomide treatment were slightly increased (changing from percentile 40 to 80 in the reference pharmacokinetics curve), whereas plasma concentrations of LPV were not affected. Follow up exams of CD4+ cells as well as HIV viral load didn't demonstrate a negative impact of lenalidomide. On the contrary, CD4+ cells showed a tendency to rise to stable levels over 230 cells/mm³.

Response to Reviewers: Dear Editor,

Please find online our revised manuscript entitled "Treatment of 5q- Syndrome with Lenalidomide in an HIV-positive patient under cART" by S. Blum et al. that we submit for publication in "Annals of Hematology" in "Letters to the Editor Section".

We changed the following points:

- 1) we added 2 figures demonstrating the changes in blood counts and lymphocyte subpopulations
- 2) the reference Giagounidis et al, Ann Hematol 2008; 87:345-52 was added to the list

3) the English style and grammar was corrected by a native speaker
Thank you very much.
Sincerely yours,

Sabine Blum

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2 Treatment of 5q- Syndrome with Lenalidomide in an HIV-positive Patient under cART
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6 To the editor

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8 Lenalidomide has emerged as standard treatment for 5q-syndrome ¹. In normal cell
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10 cultures lenalidomide enhances T-cell-proliferation ², in cells isolated from HIV-
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12 positive (HIV+) and CMV+ patients, lenalidomide enhances CD8+ cytotoxic T-cell-
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14 activity against viral antigens ³. There is no in vivo data on lenalidomide in HIV+
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16 patients.
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20 We are reporting on a 52 year old HIV+ patient with an undetectable viral load for
21
22 the past 10 years on combined antiretroviral therapy (cART) who developed 5q-
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24 syndrome and was successfully treated with lenalidomide. In 1989 he was diagnosed
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26 with HIV and had been on cART since 1996 after mono and bi-therapies. He had
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28 suffered and recovered from multiple complications (CMV-retinitis, Kaposi sarcoma,
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30 cryptococcal meningitis, oesophageal candidiasis, disseminated Mycobacterium
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32 genavense infection and anal squamous cell carcinoma (T1N0M0)). In February
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34 2007 persistent pancytopenia and dependency on red blood cell transfusions for a
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36 month motivated a bone marrow (BM) biopsy revealing a 5q-syndrome (karyotype:
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38 46,XY,del(5)(q13-14q33)[7]/46,XY[3]). In August 2007 lenalidomide was started
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40 (10mg for 21 days every 28 days) according to recommendations on the use of
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42 lenalidomide in MDS without dose reduction at any time⁴. He became transfusion
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44 independent 18 days after treatment start. After 2 cycles, complete normalisation of
45
46 peripheral blood counts was achieved (figure 1) and phlebotomy therapy was
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48 initiated for iron overload. After 5 cycles, BM examination revealed complete
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50 cytological and partial cytogenetic remission (5q deletion in 8 of 50 metaphases). HIV
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1 viral load remained undetectable before lenalidomide and 1 , 2, 3, 4, 8, 12 and 24
2 weeks after the start of lenalidomide.
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4 CD4+ cells had reached a steady state between 137 and 206 cells/mm³ previous to
5 lenalidomide. They rose to 235 cells/mm³ 2 months after starting lenalidomide and
6 remained stable between 230 and 240 cells/mm³. CD8+ cells were between 314-393
7 cells/mm³ before and reached stable levels over 500 cells/mm³ 6 weeks after
8 treatment began (527-1195 cells/mm³). Lymphocyte counts rose from 0.9-1x10⁹/l to
9 stable levels between 1.2-2.5x10⁹/l 3 months after treatment was initiated (figure 1
10 and 2).
11

12 Before lenalidomide treatment, plasma concentrations of atazanavir (ATV) and
13 lopinavir (LPV) were 1767 ng/ml and 13903 ng/ml 5 hours after last drug intake. On
14 day 23 and 28 of cycle 2 of lenalidomide treatment, plasma levels 11.5 hours after
15 last drug intake were 2728 ng/ml and 2180 ng/ml for ATV, and 7728 ng/ml and 5791
16 ng/ml for LPV, respectively. At day 20 of cycle 3, ATV and LPV plasma
17 concentrations were 2370 ng/ml and 8378 ng/ml, 11.75 hours after last drug intake.
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19 This is the first report on lenalidomide administration to an HIV+ patient with 5q-
20 syndrome without interruption of cART. Plasma levels of ATV under lenalidomide
21 treatment were slightly increased (changing from percentile 40 to 80 in the reference
22 pharmacokinetics curve), whereas plasma concentrations of LPV were not affected.
23 Follow up examination of CD4+ cells as well as HIV viral load didn't demonstrate a
24 negative impact of lenalidomide. On the contrary, CD4+ cells showed a tendency to
25 rise to stable levels over 230 cells/mm³. The CD4+ cell rise might be due to the fact
26 that lymphocytes could have been part of the MDS clone. Another reason could be
27 an immunomodulatory effect. No rise in viral load was observed, as demonstrated in
28 patients treated with thalidomide ^{5,6}.
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Although a 5q- syndrome rarely occurs in HIV+ patients, our observation is of interest as it suggests that HIV+ patients with other pathologies known to respond to lenalidomide, such as multiple myeloma for instance, could also benefit from this treatment. As thalidomide has proven to be helpful in HIV+ patients for wasting syndrome, ulcers and Kaposi's sarcoma but is sometimes impossible to continue due to adverse events, lenalidomide could also be an alternative treatment in these diseases.

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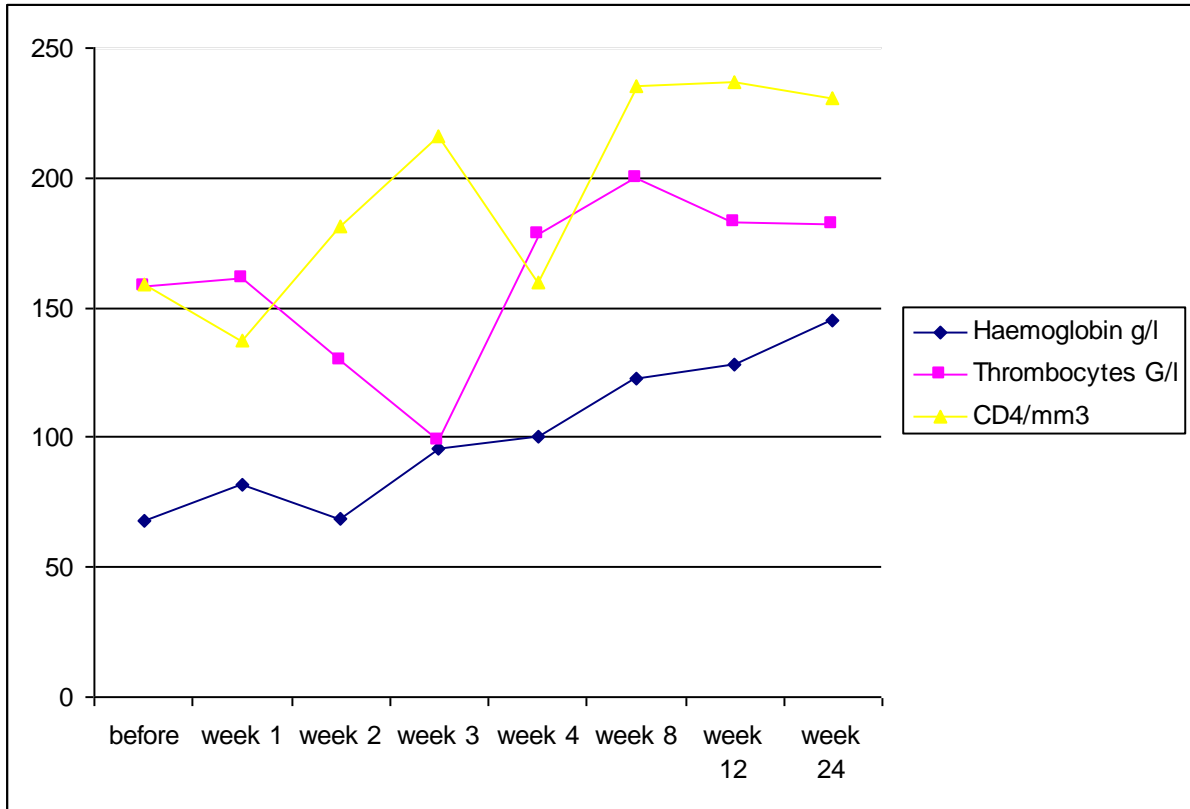


figure 1: changes in haemoglobin, thrombocytes and CD4 counts

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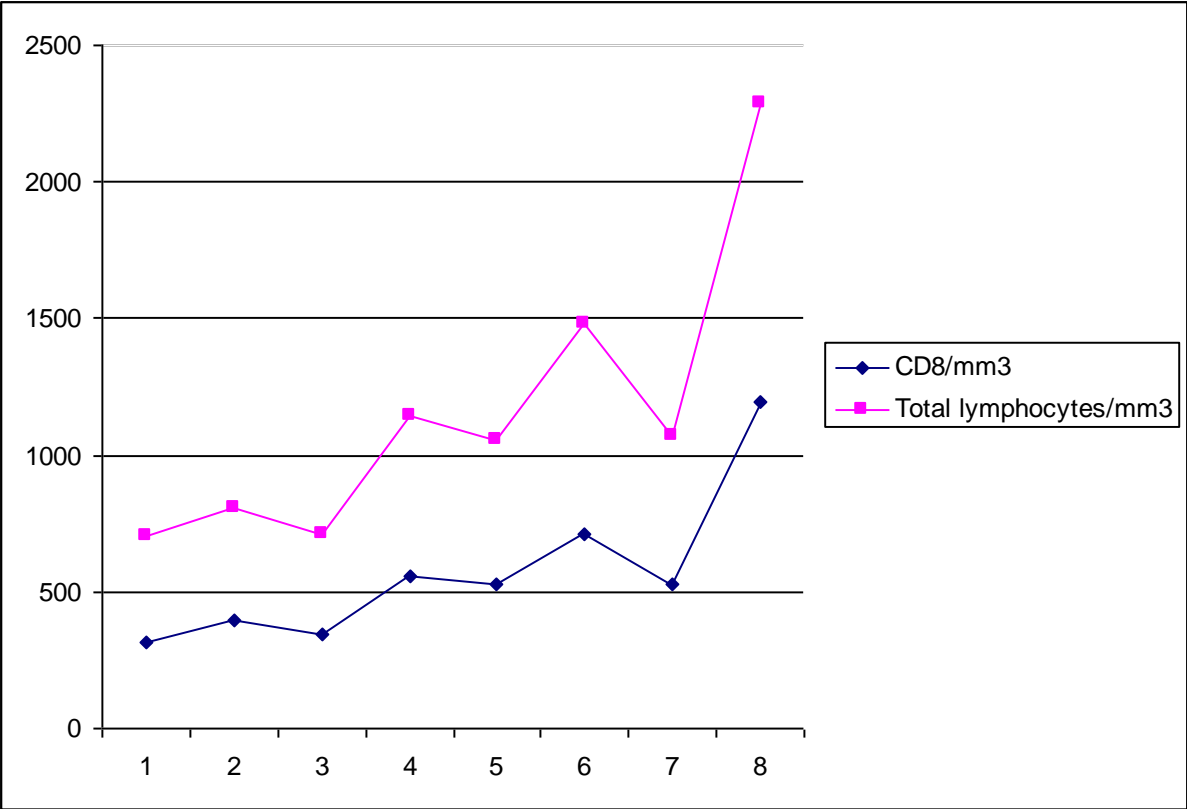


figure 2: changes CD4 and total lymphocyte counts