



Središnja medicinska knjižnica

Lucijanić M., Lasan-Trčić R., Kušec R., Pejša V., Štoos-Veić T., Jakšić O.
(2015) *Loss of response to azacitidine is associated with deletion 12p13 in a patient with myelodysplastic syndrome with unique translocation t(13;17)(q12;q25) after prior breast cancer and acute promyelocytic leukemia. Annals of Hematology, 94 (9). pp. 1617-9.*
ISSN 0939-5555

<http://www.springer.com/journal/277>

<http://link.springer.com/journal/277>

The final publication is available at Springer via
<https://doi.org/10.1007/s00277-015-2428-6>

<http://medlib.mef.hr/2758>

University of Zagreb Medical School Repository

<http://medlib.mef.hr/>

Title:

Loss of response to azacitidine is associated with deletion 12p13 in a patient with myelodysplastic syndrome with unique translocation t(13;17)(q12;q25) after prior breast cancer and acute promyelocytic leukemia

Authors:

Marko Lucijanic¹, Ruzica Lasan-Trcic^{2,3}, Rajko Kusec^{1,3,4}, Vlatko Pejsa^{1,3}, Tajana Stoos-Veic⁵, Ozren Jaksic^{1,3}

Affiliations:

¹Department of Hematology, University Hospital Dubrava, Avenija Gojka Suska 6, 10000 Zagreb, Croatia

²Department of Pediatrics, University Hospital Center Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

³University of Zagreb, School of Medicine, Salata 3, 10000 Zagreb, Croatia

⁴Clinical Institute of Laboratory Diagnosis, Division of Molecular Diagnosis and Genetics, University Hospital Dubrava, Avenija Gojka Suska 6, 10000 Zagreb, Croatia

⁵Department of Clinical Cytology and Cytometry, University Hospital Dubrava, Avenija Gojka Suska 6, 10000 Zagreb, Croatia

Corresponding author:

Ozren Jaksic

Department of Hematology, University Hospital Dubrava, Avenija Gojka Suska 6, Zagreb, Croatia

Email: ojaksic@kbd.hr

Tel: +38512903725

Keywords:

therapy related neoplasm; myelodysplastic syndrome; azacitidine

Dear editor,

With increasingly successful treatment of malignancies, therapy-related leukemia (TRL) and myelodysplastic syndrome (MDS) are increasingly observed, especially in association with prior radiotherapy, use of alkylating agents or topoisomerase-II inhibitors [1,2]. They are characterized by lesions of chromosomes 5 and 7 and poor survival (median 7-10 months) [3,4]. Azacitidine may be a reasonable treatment choice [5] although safety concerns in patients with complex cytogenetics [6] or previous acute promyelocytic leukemia (APL) exist [7]. Here we present a case of two consecutive, individually rare, TRLs following initial solid tumor and subsequent treatments with development of unique translocation (13;17)(q12;q25). Azacitidine was successfully used achieving one year long remission when patient relapsed revealing a distinctive karyotype (Figure 1).

Female patient aged 61 was diagnosed with breast cancer in 2006. She had mastectomy, received 4 cycles of doxorubicin/cyclophosphamide, 4 cycles of paclitaxel and radiotherapy accomplishing remission.

In 2009 APL was diagnosed, *PML/RAR α* positive (47,XX,+8,t(15;17)(q24;q21)[10]). Antracycline/ATRA based induction and three consolidation therapies were followed by 2 year ATRA/6-MP/methotrexate maintenance. Remission was soon achieved and patient remained without detectable *PML/RAR α* transcript thereafter.

In 2013 patient developed anemia requiring transfusion support. MDS (18% blasts) with complex cytogenetics (45,XX,del(5)(q22q33),-7,t(13;17)(q12;q25),del(12)(p13),add(20)(q11)[cp15]) was diagnosed. Azacitidine was instituted as salvage therapy and patient became transfusion independent, achieving hematological remission. After 11 cycles azacitidine had to be stopped due to development of anemia and thrombocytopenia. Repeated revisions showed increased number of blasts (15% progressing to 72%) and altered cytogenetics (45,XX,del(5)(q22q33),-7,t(13;17)(q12;q25),del(12)(p13)[20]). FISH was performed on the actual sample and retrospectively (at the time of MDS diagnosis) revealing 12p13 deletion was initially present in a subclone comprising 35% of cells and now prevailing in 90% of cells. 17p13 deletion was absent in both samples. Patient receives supportive treatment and remains alive more than 18 months since diagnosis.

Several interesting observations emerge from our case. Treatment-related malignancies represent a life-long problem reflecting underlying genome instability (obvious weak point at chromosome 17). Unique translocation (13;17)(q12;q25), has not been described in MDS before and bears unknown prognostic significance (*ZNF198*, *FLT3*, *BRCA2* and *Septin* from the rearranged chromosomal regions are possible candidate genes). Our heavily pretreated patient was successfully treated with azacitidine achieving prolonged remission. Therapy was well tolerated and no reactivation of previous APL was observed [7]. However, disease control was ultimately lost with the expansion of clone harboring deletion 12p13 (locus of *TEL/EFV6* gene) rendering azacitidine therapy ineffective. This association has not been described so far and implies potential molecular mechanisms worth investigating in further studies. No deletion of 17p13 (locus of *TP53* gene) was detected, as assessed by FISH. Lesions of *TP53* [8] and overlapping categories of monosomal and complex karyotype [4,9,10] are associated with inferior clinical outcomes in MDS patients treated with hypomethylating agents. MDS with complex cytogenetics may also represent entity of higher risk for treatment [6] as resulting genome instability and selective action of hypomethylating agents on different subpopulations may favor expansion of most resilient clone (accelerating transformation to acute leukemia). This puts treating physicians “between Scylla and Charybdis” leaving them to choose between “less of two evils”. In our opinion, due to the lack of alternative treatment options in this especially unfavorable group of patients, azacitidine is still a reasonable choice.

Conflict of Interest: O.J. and V.P. have received a speaker honorarium from Celgene. Other authors declare that they have no conflict of interest.

Informed consent: Patient gave written informed consent for all procedures and for publishing.

References:

1. Latagliata R, Petti MC, Fenu S, Mancini M, Spiriti MA, Breccia M, Brunetti GA, Avvisati G, Lo Coco F, Mandelli F (2002) Therapy-related myelodysplastic syndrome-acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem. *Blood* 99 (3):822-824
2. Leone G, Voso MT, Sica S, Morosetti R, Pagano L (2001) Therapy related leukemias: susceptibility, prevention and treatment. *Leukemia & lymphoma* 41 (3-4):255-276. doi:10.3109/10428190109057981
3. Lobe I, Rigal-Huguet F, Vekhoff A, Desablens B, Bordessoule D, Mounier C, Ferrant A, Sanz M, Fey M, Chomienne C, Chevret S, Degos L, Fenaux P, European APLge (2003) Myelodysplastic syndrome after acute promyelocytic leukemia: the European APL group experience. *Leukemia* 17 (8):1600-1604. doi:10.1038/sj.leu.2403034
4. Montesinos P, Gonzalez JD, Gonzalez J, Rayon C, de Lisa E, Amigo ML, Ossenkoppele GJ, Penarrubia MJ, Perez-Encinas M, Bergua J, Deben G, Sayas MJ, de la Serna J, Ribera JM, Bueno J, Milone G, Rivas C, Brunet S, Lowenberg B, Sanz M (2010) Therapy-related myeloid neoplasms in patients with acute promyelocytic leukemia treated with all-trans-retinoic Acid and anthracycline-based chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 28 (24):3872-3879. doi:10.1200/JCO.2010.29.2268
5. Bally C, Thepot S, Quesnel B, Vey N, Dreyfus F, Fadlallah J, Turlure P, de Botton S, Dartigeas C, de Renzis B, Itzykson R, Fenaux P, Ades L (2013) Azacitidine in the treatment of therapy related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML): a report on 54 patients by the Groupe Francophone Des Myelodysplasies (GFM). *Leukemia research* 37 (6):637-640. doi:10.1016/j.leukres.2013.02.014
6. Turturro F, Leary C, Stephens J, Veillon D, Lowery-Nordberg M (2010) Caution using hypomethylating agents in myelodysplasia or myeloid leukemia with complex cytogenetics.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology
28 (22):e380-381. doi:10.1200/JCO.2010.28.5775

7. Scaglioni PP, Cai LF, Majid SM, Yung TM, Socci ND, Kogan SC, Kopelovich L, Pandolfi PP (2011) Treatment with 5-azacytidine accelerates acute promyelocytic leukemia leukemogenesis in a transgenic mouse model. *Genes & cancer* 2 (2):160-165. doi:10.1177/1947601911410300

8. Yi JH, Huh J, Kim HJ, Kim SH, Kim SH, Kim KH, Do YR, Mun YC, Kim H, Kim MK, Kim HJ, Kim T, Kim DD (2013) Genome-wide single-nucleotide polymorphism array-based karyotyping in myelodysplastic syndrome and chronic myelomonocytic leukemia and its impact on treatment outcomes following decitabine treatment. *Annals of hematology* 92 (4):459-469. doi:10.1007/s00277-012-1635-7

9. Abaigar M, Ramos F, Benito R, Diez-Campelo M, Sanchez-del-Real J, Hermosin L, Rodriguez JN, Aguilar C, Recio I, Alonso JM, de las Heras N, Megido M, Fuertes M, del Canizo MC, Hernandez-Rivas JM (2013) Prognostic impact of the number of methylated genes in myelodysplastic syndromes and acute myeloid leukemias treated with azacytidine. *Annals of hematology* 92 (11):1543-1552. doi:10.1007/s00277-013-1799-9

10. Pleyer L, Burgstaller S, Girschikofsky M, Linkesch W, Stauder R, Pfeilstocker M, Schreder M, Tinchon C, Sliwa T, Lang A, Sperr WR, Krippel P, Geissler D, Voskova D, Schlick K, Thaler J, Machherndl-Spandl S, Theiler G, Eckmullner O, Greil R (2014) Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine Registry of the AGMT-Study Group. *Annals of hematology* 93 (11):1825-1838. doi:10.1007/s00277-014-2126-9

Fig.1

Two distinctive cytogenetic profiles (prior to and after azacitidine treatment) in a patient with therapy-related myelodysplastic syndrome and complex cytogenetics. A) Karyotype at time of diagnosis was 45,XX,del(5)(q22q33),-7,t(13;17)(q12;q25),del(12)(p13),add(20)(q11)[cp15]. Unique translocation (13;17)(q12;q25) has not been described before and bears unknown prognostic significance. Number of genes previously recognized in context of myeloid and other malignancies are candidates for rearrangement (including *ZNF198*, *FLT3*, *BRCA2* and *Septin*). B) Karyotype after loss of response to azacitidine was: 45,XX,del(5)(q22q33),-7,t(13;17)(q12;q25),del(12)(p13)[20]. Deletion 12p13 (locus of *TEL/EFV6* gene) was initially present in a subclone comprising 35% of cells and now prevailing in 90% of cells. *TEL* is strong transcriptional repressor playing crucial role in hematopoietic regulation. Deletion of 17p13 was absent in both samples. Aforementioned set of events reflects selective action of hypomethylating agents on subpopulations of cells in MDS with complex cytogenetics (eradicating subpopulation with altered chromosome 20 and favoring one with partial deletion of chromosome 12) and suggests possible molecular mechanisms of drug resistance. Legend: single horizontal arrow – del(5)(q22q33); X sign – deletion of chromosome 7; single vertical arrow – del(12)(p13); double horizontal and triple horizontal arrows – t(13;17)(q12;q25); double vertical arrow – add(20)(q11).

