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Venetoclax First Cycle Treatment in a Case of Severe AML FAB M2 and COVID-19 Pneumoniae: A Rare Clinical Scenario

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Here we describe a rare case of a venetoclax first cycle treatment in a case of a newly diagnosed COVID-19 pneumoniae.

Keywords: Post-covid syndrome; hemoptysis; thrombocytopenia; acute myeloid leukemia; SARS-CoV-2.

1. INTRODUCTION

Venetoclax is a BH3-mimetic and selective BCL-2 inhibitor and was recently approved by the Romanian Health Ministry [1] for the treatment of acute myeloid leukemia (AML) in patients. However, Romania currently remains the only EU country where the cost of Venetoclax is neither fully nor partially supported by the National Health Insurance House hence the leukemia patients have to either purchase it on their own expense or helped by compassionate

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care organizations. Venetoclax helps restoring the process of apoptosis by selectively binding to BCL-2 protein family and displacing pro-apoptotic proteins. Venetoclax is indicated for adults either over 75 years old or who have comorbidities that would not permit the use of intensive induction chemotherapy. Moreover, it is indicated to be used for the treatment of AML in adults in combination with either azacitidine or decitabine or low-dose cytarabine. In this paper we describe a very rare case of a venetoclax first cycle treatment for a patient diagnosed with COVID-19 penumoniae and show that the venetoclax treatment worked against AML.

2. PRESENTATION OF THE CASE

A 70 years old normotensive, non-diabetic male was diagnosed with endocarditis with Aerococcus Viridans as well as AML M2/FAB soon after a third molar extraction followed up by persistent fatigue, fever, weakness, nausea and excessive sweating, especially at night. By that time, he had no history of surgeries, comorbidities or any other disease. The patient was thoroughly investigated. Hemoglobin was 9.6 g/dl, with 42% Myeloblasts, 59% Neutrophils, 4% Lymphocytes, 3% Erythroblasts, 3% Metamyelocytes, 13% Myelocytes, 2% Monocytes, 3% Erythroblasts, 2% Plasmocytes and there was severe thrombocytopenia on the peripheral smear (PLT= 89 K/μL < 150K/μL). He was initially treated for endocarditis with the antibiotics teicoplanin and ceftriaxone and also had a heart valve replacement surgery with Edwards Lifescience Perimount no.25 biological valve followed by the same antibiotic treatment. No AML treatment has been performed meanwhile other than blood transfusions (for 2 months). The AML karyotype formulae was: 45, X, -Y, t(8;21)(q22; q22.1)[2]/46,XY[1] and based on the affected genes was categorized as acute myeloid leukemia with t(8;21)(q22; q22.1);RUNX1- RUNX1T1 (as per the WHO 2016 classification).

After these 2 months, he started being treated for AML with hypomethylating agents: Azacitidine 75 mg/mL for 10 cycles of 28 days, the first 9 cycles 3mLx2, the days 1-7 (14 injections per cycle) whereas the 10^{th} cycle half dose only, that is 3mL, due to the installation of biocytopenia (neutropenia and thrombocytopenia as Table 1 shows). These 10 cycles were followed by a 28-days pause while waiting on venetoclax supply to arrive and finally by one 28 day-cycle of Venetoclax combined with half dose Azacitidine. In addition, he received Tagremin (sulfamethoxazole 400 mg trimethoprim 80 mg)x2 tablets/day x 3days/week (to prevent fungal infections), as well as Acyclovir 400 mg x2 tablets/day x 3days/week (to prevent viral infections). Other blood tests results for all cycles are presented in Table 1.

10 days after starting the first venetoclax cycle, while being hospitalized in a Romanian hospital he started showing less common COVID-19 symptoms such as hemoptysis (see [3]), his blood oxygen level dropped below 95% and 3 days later he was diagnosed with COVID-19 after taking the antigen test followed by a Real Time PCR. Hemoptysis was followed starting day 6 by extreme fatigue and brain fog. The treatment had to be complex hence the patient was moved to another Romanian hospital designated for COVID-19 and also specialized in leukemia. There he started the remdesivir treatment for COVID-19 (see [4]) in combination with variconazal, doxycycline, sumetrolim (to prevent fungal infections), acyclovir (to prevent viral infections), furosemide (to avoid tumor lysis syndrome - TLS) and continued taking the venetoclax - kept at 100 mg tablet daily dose - to try to maintain a balance and protect the patient's weakened heart while fighting against both COVID-19 and AML. Meanwhile, he also received dexamethasone to protect the respiratory function as well as oxygen support. The patient lived beyond the critical days of the evolution of SARS-CoV-2 infection and his condition improved after the 8th day. However, as the COVID-19 pneumoniae does not heal in 14 days, the lungs sequelae, that is, the Post Covid Syndrome persisted (see [5] and [6]). Though the patient was still under oxygen support, after an almost 3 weeks struggle, his fluid leaking lungs failed due to acute respiratory insufficiency caused by the lungs lesions and hemorrhagic sequelae, hemoptysis abruptly reoccurring along with a drop below 90% of the blood oxygen level (hypoxemia) in the last day of life.

3. DISCUSSION

The use of venetoclax in patients with COVID-19 has not been thoroughly studied yet (see [7]). The venetoclax treatment functioned in this severe COVID-19 case, even in its first cycle and even without increasing the daily dose over 100 mg. The initial high value of monocytes (12620/μL) dropped close to the normalization threshold (2500/μL) after the 28 days period, more exactly to 2360/μL as shown in Figure 1. Neutrophils were also normalized to 1590/μL, within the normal range of [1500-8000] as shown

in Fig. 2. WBCs were also normalized from 22140/μL to 4090/μL as shown in Fig. 3. In addition, the response of leukemia is also quantified by the D-Dimer values. The D-Dimer initial value was high, 1.18 μg/mL and it got normalized along with the normalization of the leukocytes, in the end the D-Dimer value being 0.36 μg/mL hence normal D-Dimer. But more time would have still be needed under venetoclax to recover the healthy bone marrow to produce platelet precursors as severe thrombocytopenia was revealed soon before death (PLT=14000/μL). One observed that the treatment with furosemide and the hydration for the TLS prophylaxis to support the kidney in filtering out the destroyed leukemia cells was successful, the kidney responding well to prophylaxis: the patient's creatinine value was high, 1.3 mg/dL the day he was positively tested for COVID-19 and it lowered to 0.72 mg/dL after 2 weeks. The kidney responded well because it maintained a normal filtration rate, without the accumulation of toxic nitrogenous products in the body. Interleukin-6 dropped from 77 pg/mL when diagnosed with COVID-19 to 4.9 pg/mL at the end of the venetoclax cycle. One observed that the venetoclax treatment works against AML even in COVID-19 cases. Though there are studies (see [8]) showing that hydroxychloroquine (aka plaquenil) is efficient in clearing the viral nasopharyngeal carriage of SARS-CoV-2 up to six days in most COVID-19 patients and, in addition, hydroxychloroquine proved to be efficient in haematological cancers (see [9] and [10]), no hydroxychloroquine was used during the treatment. The current data on the epidemiology of the COVID-19 pandemic can be found at (see [11]).

Ghandili et al. [12] have described 12 cases of acute leukemia and COVID-19 patients, out of which 8 patients (67%) had acute myeloid leukemia (AML) and 4 patients (33%) had acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL). The median age of the patients was 60 years (range: 32-76) and seventy-five percent were male. Out of the 8 AML patients 3 had newly diagnosed untreated AML, 4 had refractory/relapsed AML and one patient was in complete remission with incomplete hematologic recovery (CRi). The latest one received high-dose cytarabine for the consolidation therapy and died 3 weeks after the COVID-19 infection due to severe acute respiratory distress syndrome (ARDS). Their finding was that all 3 AML patients with newly diagnosed AML developed severe ARDS. However, the only one treated with intensive chemotherapy died. In addition, none of the 4 refractory AML patients treated with azacitidine/venetoclax developed ARDS.

Ferra F et al. [13] describe the treatment outcome of ten consecutive COVID-19 patients with AML their median age being 60 (range: 31–69) and M/F ratio 5/5. Two patients were newly diagnosed, 6 in complete remission (CR) and 2 in relapse. In their study, COVID-19 imposed hematological treatment modifications in 7 patients. However one died before any treatment, 3 discontinued the therapy (venetoclax/azacitidine and venetoclax/enasidenib in 2 relapsed patients) and high-dose cytosine-arabinoside as first consolidation in one CR patient. Out of the 10 patients, 7 encountered abrupt worsening of the respiratory function. Five patients (50%) died after a median time of 8 days.

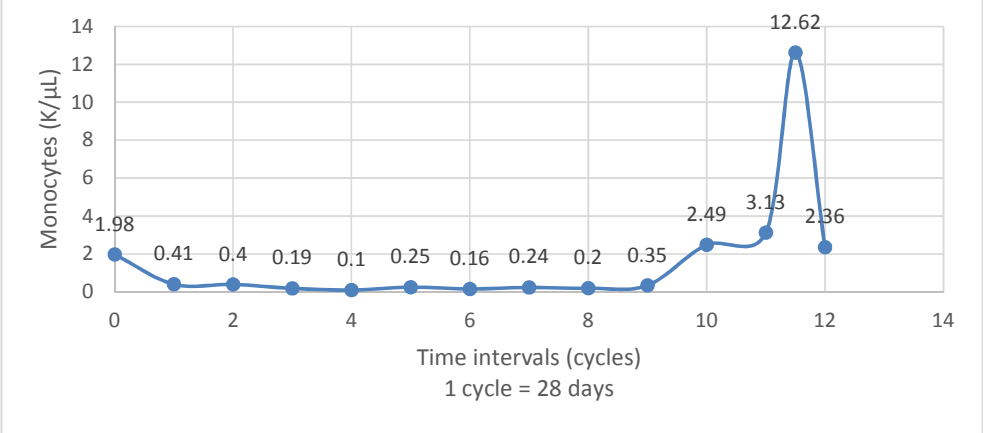

Fig. 1. Effect on monocytes of 10 cycles of azacitidine followed by a pause of one cycle and one cycle of venetoclax combined with azacytidine

Table 1. Component results since diagnosed with AML

	Month		Cycle													
Component	**1**	**2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**Unit**
WBC	4.09	6.03	3.85	3.51	2.86	1.40	1.95	2.01	2.25	2.18	2.12	4.68	6.29	22.14	4.09	K/µL
RBC	2.53	2.61	2.45	2.55	2.59	3.31	3.66	3.66	3.99	4.05	4.11	3.42	3.32	2.88	2.69	M/µL
HGB	8.6	9.3	8.4	9.6	10.6	12.9	13.5	12.9	13.8	13.6	14	11.7	11.6	9.3	8.4	g/dL
HCT	26.2	27.8	25.6	28.2	30.5	37.5	38.8	37.3	39.2	40.1	40.7	33.4	33.6	27.1	24.8	%
MCV	103.6	106.5	104.5	110.6	117.8	113.3	106	101.9	98.2	99	99	97.7	101.2	94.1	92.2	fL
MCH	34	35.6	34.3	37.6	40.9	39.0	36.9	35.2	34.6	33.6	34.1	34.2	34.9	32.3	31.2	pg
MCHC	32.8	33.5	32.8	34	34.8	34.4	34.8	34.6	35.2	33.9	34.4	35	34.5	34.3	33.9	g/dL
PLT	89	48	74	121	145	179	189	192	180	161	115	70	58	8	14	K/µL
RDW-CV	18.4	21.2	21.9	23.3	15.6	11.9	12	12.7	13.6	15.0	16.1	16.8	17.3	17.9	15.9	%
PDW	8.3	9.3	10.2	9	9.1	10.2	10.6	12.3	13.6	11.6	10.3	11.2	12.2	13.2	9.7	fL
MPV	8.9	10	10.1	9.7	9.2	10	10	10.6	11.1	10.5	10.2	10.1	10.2	11.6	9.5	fL
PCT	0.08	0.1	0.1	0.1	0.13	0.18	0.19	0.2	0.2	0.17	0.1	0.1	0.06	0	0	%
NRBC	0	0	0	0.3	0	0	0.5	0	0	0	0	0.2	0.01	0.05	0	%
NEUT	2.85	2.58	2.31	2.2	2.1	0.78	1.06	1.2	1.24	1.25	1.03	1.07	1.97	8.39	1.59	K/µL
NEUT%	69.8	42.8	60	62.7	73.5	55.8	54.4	59.7	55.2	57.3	48.5	22.9	31.3	37.90	38.9	%
LYMPH	0.66	1.46	1.12	0.91	0.56	0.52	0.61	0.62	0.73	0.7	0.72	1.09	1.14	1.11	0.14	K/µL
LYMPH%	16.1	24.2	29.1	25.9	19.6	37.1	31.3	30.8	32.4	32.1	34	23.3	18.1	5	3.4	%
MONO	0.57	1.98	0.41	0.4	0.19	0.1	0.25	0.16	0.24	0.2	0.35	2.49	3.13	12.62	2.36	K/µL
MONO%	13.9	32.8	10.6	11.4	6.6	7.1	12.8	8	10.7	9.2	16.5	53.2	49.8	57	57.7	%
EO	0	0	0	0	0	0	0.01	0.01	0.01	0.01	0.01	0	0.01	0	0	K/µL
EO%	0	0	0	0	0	0	0.5	0.16	0.4	0.5	0.5	0	0.2	0	0	%
BASO	0.01	0.01	0.01	0	0.01	0	0.02	0.02	0.03	0.02	0.01	0.03	0.04	0.02	0	K/µL
BASO%	0.2	0.2	0.3	0	0.3	0	1	1	1.3	0.9	0.5	0.6	0.6	0	0	%
IG	0.4	0.78	0.4	0.19	0.18	0.09	0.05	0.02	0.04	0.09	0.14	0.55	0.85	1.04	0.31	K/µL
IG%	9.8	12.9	10.4	5.4	6.3	6.4	2.6	1	1.8	4.1	6.6	11.8	13.5	4.7	7.6	%

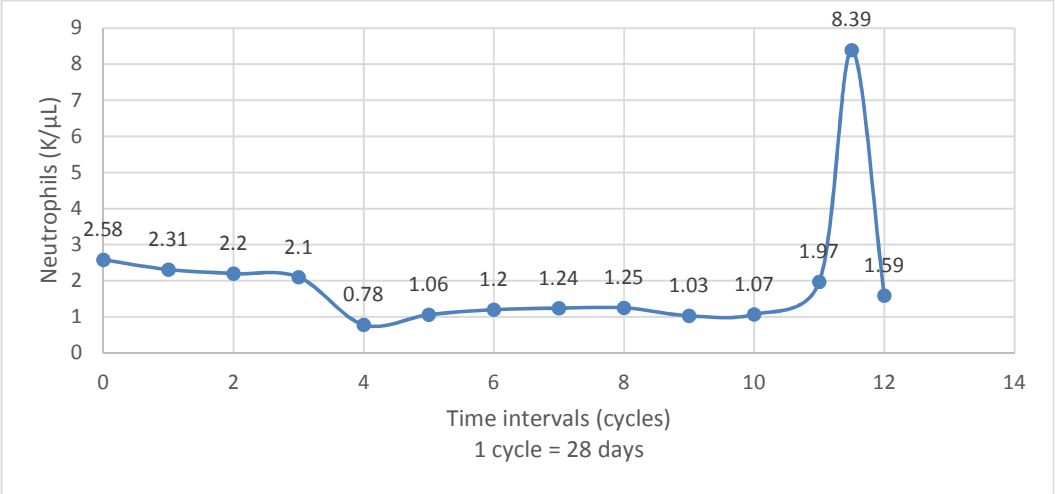

Fig. 2. Effect on neutrophils of 10 cycles of azacitidine followed by a pause of one cycle and one cycle of venetoclax combined with azacitidine

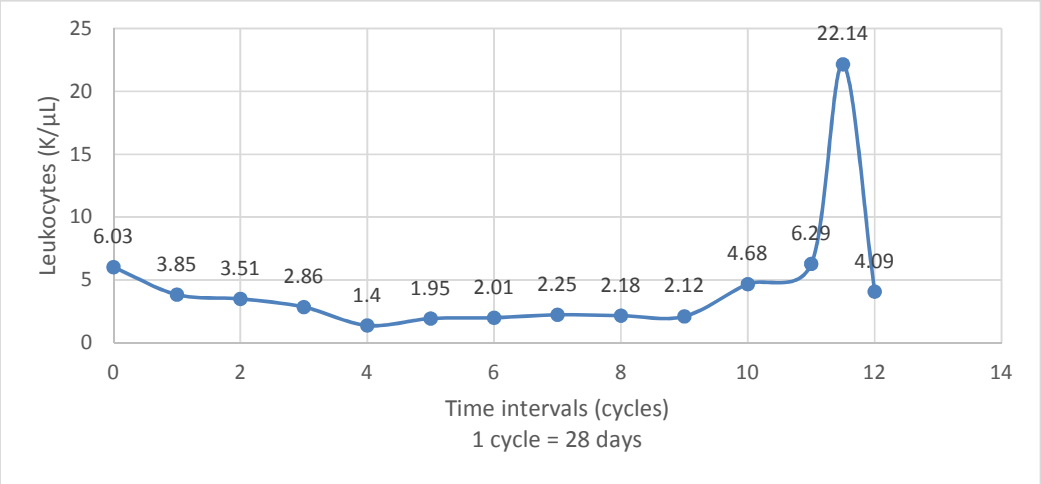

Fig. 3. Effect on leukocytes of 10 cycles of azacitidine followed by a pause of one cycle and one cycle of venetoclax combined with azacitidine

SARS-CoV-2 infection has a major impact on AML patients survival and as also described in the current paper, most patients with acute leukemia develop a severe form of COVID-19. Similarly, Passamonti et al. [14] emphasize the need for aggressive infection prevention strategies in one of the largest studies for patients with haematological malignancies and COVID-19 due to their increased risk of mortality (536 enrolled patients out of which 198, that is 37%, died).

NHS England has granted emergency approval of venetoclax and gilteritinib for leukemia patient groups (see [15]). The Leukemia-specific risk factors for COVID-19 as well as treatment alternatives and guidelines for patients with leukemia during COVID-19 high-risk periods are presented in [16] and [2].

Mortality in patients with AML and risk factors can be also consulted in [17] and [18]. The study [19] revealed the fact that among patients with AML, 46.9% did not survive the COVID-19.

4. CONCLUSION

Venetoclax first cycle treatment in SARS-CoV-2 infected patients is a very rare case. As described in this paper, the venetoclax treatment worked against AML in this COVID-19 case. However, in the event this patient would have not

been infected with SARS-CoV-2, due to his response to venetoclax, his life expectance would have been over 12 months with a probability of about 75% (see [20]) in which case he would have continued with the next phases of the venetoclax treatment with a high probability of living at least 18 more months as per [20], the median overall survival rate being 14.7 months ([21]).

CONSENT

The author declares that written informed consent was obtained from the patient for publication of this case report and accompanying images. As per international standard, patient's written consent has been collected and preserved by the author.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the author.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Ministry of Health of Romania, Official Journal of Romania, Annex 1 to the Order of the Minister of Health no.1/301/500/ Romanian. 2008:1-43.
Accessed 31 December 2020.
Available:http://www.ms.ro/wp-content/uploads/2018/06/Ordin-privind-aprobarea-protocoalelor-terapeutice-1.pdf
2. Zeidan A, Boddu P, Patnaik M, Bewersdorf J, et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: Recommendations from a panel of international experts, Lancet. 2020;7(8):601-612.
Available:https://doi.org/10.1016/S2352-3026(20)30205-2
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223): 497-506.
DOI: 10.1016/S0140-6736(20)30183-5
Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30; PMID: 31986264; PMCID: PMC7159299.
4. European Commision, European Commission secures EU access to Remdesivir for treatment of COVID-19; 2020.
Accessed 31 December 2020.
Available:https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1416
5. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19, Jama. 2020;324(6):603-605.
DOI: 10.1001/jama.2020.12603
Available:https://pubmed.ncbi.nlm.nih.gov/32644129/
6. Tenforde M, Kim S, Lindsell C, Rose E, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March–June 2020, MMWR Morb Mortal Wkly Rep. 2020;69(30):993–998.
DOI: 10.15585/mmwr.mm6930e1
7. Venclexta, Prescribing Information CORONAVIRUS/COVID-19 and VENCLEXTA® (VENETOCLAX); 2020.
Available:https://www.venclextahcp.com/covid-19.html
8. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.
DOI: 10.1016/j.ijantimicag.2020.105949
Epub 2020 Mar 20. PMID: 32205204; PMCID: PMC7102549.
9. Han B, Zhao Y, Lin Y, Fu S, Wang L, Zhang M, et al. Hydroxychloroquine sensitizes chronic myeloid leukemia cells to Vγ9Vδ2 T cell-mediated lysis independent of autophagy. Int J Oncol. 2017;50(5):1810-1820.
DOI: 10.3892/ijo.2017.3934
Epub 2017 Mar 24. PMID: 28339029.
10. DrugBank. Hydroxychloroquine Terminated Phase 1 Trials for Acute Myeloid Leukemia (AML) Treatment,
Available:https://go.drugbank.com/drugs/DB01611/clinical_trials?conditions=DBCON

D0034998&phase=1&purpose=treatment&status=terminated

11. Coronavirus Research Center, John Hopkins University, Covid-19 dashboard for systems science and engineering; 2020.
Available:https://coronavirus.jhu.edu/map.html
12. Ghandili S, Pfefferle S, Roedl K, Sonnemann P, et al. Challenges in treatment of patients with acute leukemia and COVID-19: A series of 12 patients, Blood Adv. 2020;4(23):5936–5941.
DOI: 10.1182/bloodadvances.2020002543
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7724904/
13. Ferrara F, Zappasodi P, Roncoroni E, Borlenghi E, et al. Impact of Covid-19 on the treatment of acute myeloid leukemia. Leukemia 34. 2020;2254–2256.
Available:https://doi.org/10.1038/s41375-020-0925-7
14. Passamonti F, Cattaneo C, Arcaini L, Bruna R, et al. MD clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: A retrospective, multicentre, cohort study, Lancet. 2020;7(10):737-745.
Available https://doi.org/10.1016/S2352-3026(20)30251-9
Available:https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30251-9/fulltext
15. AML Working Party COVID-19 Recommendations; 2020 in Press.
Available:http://www.cureleukaemia.co.uk/page/news/523/aml-working-party-covid-19-recommendations
16. Paul S, Rausch C, Jain N, Kadia T, et al. Treating Leukemia in the Time of COVID-19. Acta Haematol; 2020.
DOI: 10.1159/000508199
Available:https://www.karger.com/Article/FullText/508199#
17. Fattizzo B, Giannotta JA, Sciumè M, et al. Reply to "COVID-19 in persons with haematological cancers": A focus on myeloid neoplasms and risk factors for mortality. Leukemia. 2020:34, 1957–1960.
Available:https://doi.org/10.1038/s41375-020-0877-y
18. He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, et al. COVID-19 in persons with haematological cancers. Leukemia. 2020;34:1637–1645.
Available:https://doi.org/10.1038/s41375-020-0836-7
19. Alicea J. COVID-19 and hematological diseases linked to high mortality rate, conference, American Society of Hematology; 2020.
Accessed 6 December 2020.
Available:https://www.hcplive.com/view/covid19-hematological-diseases-linked-high-mortality-rate
20. Knight T, Edwards H, Taub J, Ge Y. Evaluating venetoclax and its potential in treatment-naïve acute myeloid leukemia, Cancer Management and Research. 2019;11:3197-3213.
DOI: 10.2147/CMAR.S180724
21. Venclexta, AML Information; 2020.
Available:https://www.venclextahcp.com/aml.html

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