Case series of complex therapy of hemoblastosis in the context of COVID-19.

Vadim Kemaykin[1], Ruzal Vildanova[1], Azat Karabekov[1], Jamilya Saparbay[1], and Zhandos Byrkitbayev[1]

[1]National Research Oncology Center

March 30, 2022

Abstract

The novel COVID-19 spread around the world.Patients with malignant neoplasms are more susceptible to infection.Here we presents clinical cases of complex therapy of patients with with hemoblastosis and concomitant COVID-19 infection

Title: Case series of complex therapy of hemoblastosis in the context of COVID-19

Running tittle: Case series of complex therapy of hemoblastosis in the context of COVID-19.

Kemaykin, V.M.[1], Vildanova, R. F.[1], Saparbay J.Zh.[1,]

Karabekov, A.B.[1]Burkitbayev Zh. K.[1]

[1] - LLP «National Research Oncology Center»

Department of oncohematology and Bone Marrow Transplantation

Keywords: COVID-19, hemoblastosis, multiple myeloma, chemotherapy, autologous stem-cell transplantation, acute myeloid leukemia

Key clinical message: The novel COVID-19 spread around the world. Patients with malignant neoplasms are more susceptible to infection. Here we presents clinical cases of complex therapy of patients with hemoblastosis and concomitant COVID-19 infection

CORRESPONDING AUTHOR: Ruzal Vildanova

EMAIL: Ruzal_Vildanova@mail.ru

TELEPHONE: 8 (7172) 70 29 41

Email: hema.dep2016@gmail.com

Fax: -8-717-2-70-29–41

Telephone: 8-717-2-70-29–41

Index: 010000

COVID-19 - coronavirus disease 2019

SARS-CoV-2 - severe acute respiratory syndrome related coronavirus 2

CT - computed tomography

NROC - National Research Oncology Center LLP

CRAB - mnemonic abbreviation: hyperCalcemia; Renal insufficiency; Anemia; Bone lesions

CTX - chemotherapy

IMWG - International Myeloma Working Group

Auto-SCT - autologous stem-cell transplantation

BMT - bone marrow transplantation

GCS - glucocorticosteroid

NIV - non-invasive ventilation of the lungs

PCR - polymerase chain reaction

ABT - antibiotic therapy

CRP - c-reactive protein

Introduction

The novel coronavirus infection COVID-19 led to an outbreak at the end of December 2019 in the Chinese city Wuhan, which quickly spread around the world. In March 2020, the World Health Organization announced a pandemic of the new coronavirus SARS-CoV-2 and pneumonia it causes, COVID-19. Currently, 40,567,780 cases of coronavirus infection and more than 1,123,127 deaths have been registered in the world (1). In Kazakhstan, the first case of coronavirus infection was registered in March 2020; for October 2020, 109 623 cases of infection, 1768 deaths were registered (2).

Cohorts of older people and people with weakened immune systems are at higher risk of contracting coronavirus infection (3). Patients with hematological diseases, especially malignant neoplasms, are more susceptible to infection than the general population due to the systemic immunosuppression administered as part of the treatment of the underlying disease. Therapy is accompanied by neutropenia, lymphopenia, and disorders of the mechanisms of innate and adaptive immunity, as well as the influence of chemotherapy and other methods of treatment. Consequently, patients with hematologic malignancies may be at increased risk of contracting COVID-19 and have a worse prognosis. These patients can also spread the virus for a longer time due to the increased viral load and delayed elimination of the virus (4).

In world practice, enough experience has not yet been accumulated in the treatment of hemoblastosis in the context of COVID-19, recommendations in this direction are based on the opinion and experience of experts and are constantly updated (5).

1. Clinical case

A 47-year-old female patient was diagnosed with multiple myeloma, which debuted with pain in the lumbar spine and right shoulder joint. In dynamics, despite symptomatic therapy, the pain intensified. According to computed tomography (CT), multiple foci of the destruction of the bones of the thoracic spine, I and VII thoracic vertebrae with a soft tissue component of 1.0-1.3cm, foci of the destruction of the sternum, scapula on the right with a soft tissue component measuring 1.0*1.3cm, and foci of the destruction of the sacrum and iliac bones were observed.

Investigation

In September 2019, the patient was admitted to the Department of Oncohematology of the National Research Oncology Center LLP (NROC). According to the results of the examinations, the following was noted: the secretion of paraprotein represented by Lambda chains (the concentration of paraprotein is 0.4 g (0.7%)) and Bens-Jones protein in urine; according to the cytological study of bone marrow, an increase in the

number of plasma cells was noted up to 23%. The patient also had CRAB (mnemonic abbreviation: hyperCalcemia; Renal insufficiency; Anemia; Bone lesions) symptomatology (moderate anemia, a widespread other-destructive process with a soft tissue component). Considering the above, the patient was diagnosed with multiple myeloma (6).

Treatment

The patient underwent 5 courses of chemotherapy (CTX) according to the "VCD" scheme. Based on the results of control restaging, the patient was found to have stabilized the underlying disease according to the IMWG (International Myeloma Working Group) criteria (plasma cell infiltration remained up to 22%) (7). It was decided to conduct 2 courses of chemotherapy according to the "TCD" scheme (Thalidomide + Cyclophosphamide + Dexamethasone).

Then the patient underwent 2 courses of chemotherapy according to the DR-PACE scheme (Dexamethasone / lenalidomide / cisplatin / doxorubicin / cyclophosphamide / etoposide) (8,9). However, despite the intensive courses, the patient, according to the cytological study of the bone marrow, retained plasma cell infiltration up to 28%. Due to the lack of effect on the ongoing therapy, the question of choosing a treatment method was discussed. We feared that other courses of chemotherapy could accumulate toxicity, thereby increasing the risk of failed hematopoietic stem cell (HSC) mobilization and bone marrow failure. Considering these factors, the patient decided to undergo Auto-SCT (autologous hematopoietic stem cell transplantation).

The patient underwent mobilization of peripheral HSCs. "Etoposide 375mg/m2 +G-CSF" was prepared in the amount of CD34 +=9.23mln / kg, which is sufficient for Auto-SCT. The patient was discharged for the recovery period. In June 2020, the patient was admitted to the Department of Oncohematology and Bone Marrow Transplantation for Auto-SCT (BMT). At the time of receipt, she had no active complaints. On July 2, 20, high-dose chemotherapy (MEL 200 mg/m2) was implemented, followed by transplantation of autologous hematopoietic stem cells in the amount of 5.58 million/kg. At +17D, the patient developed complications such as febrile neutropenia and probable invasive pulmonary aspergillosis; antifungal therapy with voriconazole and antibacterial therapy with piperacillin-tazobactam were prescribed. At +25D, bone marrow non-engraftment was recorded (0.5 thousand/μl). The general condition deteriorates sharply, acute respiratory failure develops, respiratory rate (RR) up to 36 per minute, saturation (SpO2), against the background of oxygen insufflation of 10 liters per minute - 90-91%), persistent fever, unproductive cough. On computed tomography of the lungs, subtotal infiltration from both sides is noted (involvement of the lung parenchyma on both sides is about 60%). On day 28 after transplantation, SARS-CoV-2 RNA from a nasopharyngeal smear was detected by PCR. The treatment was supplemented with anticoagulant therapy with heparin, glucocorticosteroid therapy (GCS) with dexamethasone 12 mg per day, as well as NIV (non-invasive ventilation of the lungs) in CPAP mode with FiO2 = 65%, a change in body position was performed, on the stomach - prone position. When assessing blood parameters, deep cytopenia was noted (due to the absence of bone marrow engraftment), which significantly worsened the course of the disease.

In dynamics, against the background of the ongoing complex therapy, the patient's condition improved, in the form of a decrease in signs of respiratory failure, restoration of blood counts. Control computed tomography of the chest organs showed positive dynamics, a decrease in the size of infiltration in the lungs, the volume of lung lesions was 40% (Figure 1), recovery of blood parameters (neutrophilic engraftment was noted) (Table 1). However, despite the clinical improvement, the patient, according to PCR data for COVID-19 from a nasopharyngeal smear, from 08.12.2020 and 08.26.2020, SARS-CoV-2 RNA remained. And 09.02.2020 (+62D), according to PCR-RNA SARS-CoV-2 from a nasopharyngeal smear, the infection was not detected. In this regard, at +64D after Auto-BMT, the patient was discharged from the hospital with improvement, with a relief of signs of coronavirus infection.

2. Clinical case

A 54-year-old patient was diagnosed with acute myeloid leukemia complicated by coronavirus infection, which debuted with changes according to the general blood count in the form of severe anemia, thrombocytopenia, leukocytosis, and blastemia. There were also changes according to the results of PCR for COVID-19 –

SARS-CoV-2 RNA was detected from a nasopharyngeal smear.

Investigation

In August 2020, the patient was admitted to the KVI-1 department (oncohematology N1 with resuscitation) of NROC LLP. As a result of the examination of the hemogram, cytology, and immunophenotyping, a decrease in hemoglobin and platelets, an increased level of leukocytes, the presence of tumor cells (blasts) in the peripheral blood and bone marrow were noted. When examining for PCR a nasopharyngeal smear for COVID-19, CT of the thoracic segment, the presence of positive PCR analysis, and changes in the CT picture of the type of ground glass were found. Taking into account the above, the patient was exposed to the main clinical diagnosis: "Acute myeloblastic leukemia" (10) with a concomitant diagnosis of "coronavirus infection COVID-19", bilateral polysegmental pneumonia.

Treatment

The patient underwent a chemotherapy course according to the "7+3DNR 60 mg/m2" scheme. Besides, for the treatment of COVID-19, he received a glucocorticosteroid with dexamethasone 8 mg per day, heparin therapy, as well as NIV in the CPAP mode with FiO2=70%, a change in body position was carried out on the stomach with ventilation.

Also, the patient had persistent fever, an increase in CRP and procalcitonin levels, the condition was regarded as febrile neutropenia, given which ABT (antibiotic therapy) piperacillin-tazobactam 4.5g IV 4p/s was prescribed, against the background of this therapy, the condition with improvement, in the form of a decrease in body temperature and CRP over time. At +12D after a course of chemotherapy, repeated bend of fever, an increase in CRP in dynamics, in connection with which ABT was replaced by meropenem 1.0 g IV 3p/s. In dynamics, against the background of the ongoing complex therapy, the patient's condition improved, in the form of a decrease in signs of respiratory failure, a tendency to restore blood counts (Table 2). With the control PCR COVID-19 at +19D after chemotherapy, no infection was detected, however, according to the control computed tomography of the chest, negative dynamics was noted in the form of an increase in infiltration in the lungs (Figure 2).

According to the results of control puncture at +14D, blastosis remained at 50%, remission was not achieved. Continuation of chemotherapy is indicated, to which the patient did not consent.

The patient was discharged from the hospital with no remission of the underlying disease, requiring continuation of treatment and relief of signs of coronavirus infection.

Methods

From June to October 2020, based on the oncohematological department of the National Research Oncology Center LLP, 19 patients were treated, of which: men - 11, women - 8. The average age of 43 years (+-16). Of these, patients with multiple myeloma-32%; acute myeloid leukemia - 26%; acute promyelocytic leukemia - 11%; acute lymphoblastic leukemia - 26%; chronic lymphocytic leukemia - 5%. Treatment was carried out following the protocols for the diagnosis and treatment of hemoblastosis and concomitant COVID-19 infection (11).

Discussion

Leukemia is a heterogeneous group of malignant clonal diseases of the hematopoietic tissue belonging to the group of hemoblastoses. Pathological disorders in the bone marrow lead to secondary immunodeficiency, as a result of which the disease becomes systemic.

According to Chinese researchers, patients with cancer have worse outcomes from COVID-19, which suggests that this group should be given more attention (12). Three main strategies are proposed for patients with cancer during the COVID-19 pandemic and in the event of severe infectious complications. First, in endemic regions, consideration should be given to deferring chemotherapy and routine hospitalization. Secondly, more stringent personal protection measures for cancer patients should be envisaged. Third, more intensive

monitoring or treatment should be considered when patients are infected with SARS-CoV-2 (12). The department for the treatment of patients with hematological malignancies with concomitant COVID-19 has been operating since June 2020. During this period, 19 patients were treated, of which: men - 11, women - 8. The average age was 43 years (+-16). Of these, patients with multiple myeloma-32%; acute myeloid leukemia - 26%; acute promyelocytic leukemia - 11%; acute lymphoblastic leukemia - 26%; chronic lymphocytic leukemia - 5%. In our center, we have chosen the tactics of conducting complex therapy for patients with hemoblastosis and hematopoietic depression with COVID-19 without interrupting chemotherapy. According to our preliminary observation, chemotherapy does not worsen the course of COVID-19 and does not increase early mortality after chemotherapy.

Conclusion

At the moment, there is not enough research to scientifically substantiate one or another approach to the treatment of patients with hemoblastosis and coronavirus infection. In our experience, we evaluated the effect of complex therapy in patients with hematopoietic malignancies and depression of hematopoiesis with COVID-19, without interrupting chemotherapy. The proposed protocol will presumably reduce the risks of recurrence and refractoriness of the underlying disease. Because of the above, the tactics of managing patients with hematological malignancies in the context of COVID-19 requires further study, which we plan to do in the future.

Conflict of interest

The authors declare no conflicts of interest that might bias this work.

Acknowledgements

We would like to thank the patients for allowing us to share the details of their treatment in this paper.

Author's contributions

Kemaykin, V.M – constructed the idea of manuscript; planned the methodology of the project; organized and supervised the course of the project; wrote the manuscript.

Vildanova, R. F- constructed the idea of manuscript; planned the methodology of the project; organized and supervised the course of the project; wrote the manuscript.

Saparbay J.Zh. - wrote the manuscript; edited the manuscript**.**

Karabekov A. B. - data collection; data interpretation and analysis; wrote the manuscript.

Burkitbayev Zh. K- organized and supervised the course of the project; wrote the manuscript.

Reference list

1. Worldometer, 2020. COVID-19 Coronavirus Pandemic. URL:*https://www.worldometers.info/coronavirus/v.* Accessed October 20, 2020.
2. Kazinform, 2020. COVID-19 Эпидемия коронавируса. URL:*https://www.coronavirus2020.kz.* Accessed October 20, 2020.
3. Zhu WJ, Wang J, He XH, Qin Y, Yang S, Hu XS, Wang HY, Huang J, Zhou AP, Ma F, Shi YK, Zhou SY. [The differential diagnosis of pulmonary infiltrates in cancer patients during the outbreak of the 2019 novel coronavirus disease]. Zhonghua Zhong Liu Za Zhi. 2020 Apr 23;42(4):305-311. Chinese. doi: 10.3760/cma.j.cn112152-20200303-00166. PMID: 32133833.
4. Robert Weinkove, Zoe K McQuilten, Jonathan Adler, Meera R Agar, Emily Blyth, et al., ≪Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance¿¿*Wiley Public Health Emergency Collection* 2020 Jun; 212(10): 481–489

5. Curigliano G, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, Haanen J, Jordan K, Lordick F, Machiels JP, Michielin O, Peters S, Tabernero J, Douillard JY, Pentheroudakis G; Panel members. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol. 2020 Oct;31(10):1320-1335. doi: 10.1016/j.annonc.2020.07.010. Epub 2020 Jul 31. PMID: 32745693.

6. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. Am Soc Clin Oncol Educ Book. 2016;35:e418-23. DOI: 10.1200/EDBK_159009. PMID: 27249749.

7.

https://www.nccn.org/

Dadacaridou M, Papanicolaou X, Maltesas D, Megalakaki C, Patos P, Panteli K, Repousis P, Mitsouli-Mentzikof C. Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) for relapsed or refractory multiple myeloma patients. J BUON. 2007 Jan-Mar;12(1):41-4. PMID: 17436400. Srikanth M, Davies FE, Wu P, Jenner MW, Ethell ME, Potter MN, Shaw BE, Saso RM, Dines S, Morgan GJ. Survival and outcome of blastoid variant myeloma following treatment with the novel thalidomide containing regime DT-PACE. Eur J Haematol. 2008 Dec;81(6):432-6. doi: 10.1111/j.1600-0609.2008.01131.x. Epub 2008 Aug 6. PMID: 18691254. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. doi: 10.1182/blood-2016-03-643544. Epub 2016 Apr 11. PMID: 27069254. Клинический протокол МЗ РК «Коронавирусная инфекция - COVID-19», 10-я редакция с изменениями от 15.07.2020г Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* . 2020;21(3):335-337. DOI:10.1016/S1470-2045(20)30096-6

Figure 1

Bilateral polysegmental pneumonia. Foci of destruction of the spinal column and bones of the thoracic segment (myeloma).

CT signs of bilateral interstitial pneumonia, probably of viral etiology. Foci of destruction of the thoracic vertebra and chest (myeloma) In comparison with the CT scan from 07/27/2020, there is a decrease in the size of infiltration in the lungs

Table 1

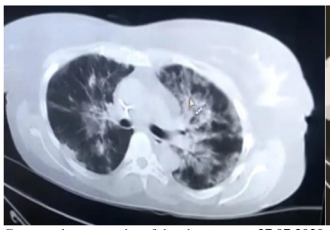
Changes in peripheral blood parameters by day from the moment of autologous bone marrow transplantation. Against the background of the complex therapy of hemoblastosis and COVID-19, an increase in the level of leukocytes is observed and bone marrow engraftment is noted.

Figure 2

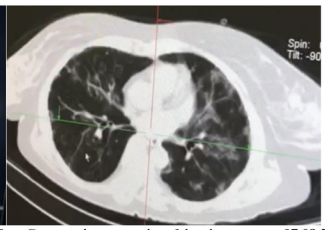
Bilateral polysegmental pneumonia, bilateral hydrothorax. In comparison with the CT scan of 08.21. there is an increase in the degree of infiltration and the development of bilateral hydrothorax.

Table 2

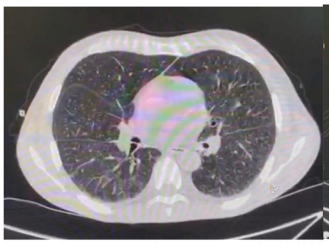
Changes in peripheral blood parameters by day from the start of therapy. Against the background of the complex therapy of hemoblastosis and COVID-19, a decrease in leukocytosis is noted, up to agranulocytosis, followed by an increase in leukocyte counts.

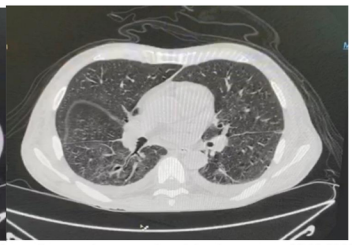


Computed tomography of the chest organs **27.07.2020r**



Computed tomography of the chest organs **07.08.2020r**


Computed tomography of the chest organs **21.08.2020**r


Computed tomography of the chest organs **28.08.2020**r

Hemogram day	+14Д	+18Д	+27Д	+29Д	+31Д	+34Д	+36Д	+57Д	+61Д
WBC	0,1	1,6	0,6	0,3	0,1	0,3	1,7	2,4	2,8
Hb	69	65	101	95	85	74	59	62	67
PLT	11	5	44	20	68	16	34	42	56

Hemogram day	**06.08**	**11.08**	**18.08**	**21.08**	**26.08**	**01.09**
WBC	45	4	0,4	0,6	0,8	1,3
Hb	50	62	63	37	67	50
PLT	11	23	17	5	17	32