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The clinical impact of COVID-19 epidemic in the hematologic setting

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ABSTRACT

The rapid onset and worldwide spread of the COVID-19 epidemic (caused by SARS-CoV-2 coronavirus) has been associated with a profound impact in clinical practice also in the hematologic setting. First of all, given the immunosuppressive effect of many therapies that are normally administered to patients with hematological diseases, with a consequent increased risk of contracting a more severe viral infection, it has been necessary to reconsider in each individual patient the urgency and priority of the treatments foreseen by the normal standards of care. In particular, as regards allogeneic (and to a lesser extent autologous) hematopoietic cell transplantation and CAR T-cell therapy, specific recommendations have been issued by the transplant community on the criteria to be used to decide whether or not to postpone these procedures and on the clinical management of recipients and donors exposed to COVID-19. As to cytotoxic chemotherapy and other antineoplastic therapies, criteria have been proposed to decide, in the various clinical situations, which treatments were not deferrable and which instead could be postponed or replaced by less aggressive therapies. In the outpatient clinics, various organizational solutions for telemedicine have been adopted, resorting to telephone interviews and/or Information Technology, with the aim of reducing the influx of patients while maintaining an adequate control of their clinical condition. The collection of blood by the transfusion centers has been the subject of organizational measures, in order to avoid the transmission of COVID 19 while maintaining a sufficient blood collection for clinical needs. Finally, some hematologic laboratory alterations have been identified, such as thrombocytopenia, lymphopenia and coagulation abnormalities, useful for the prognostic evaluation of infected patients.

1. Introduction

The rapid onset and worldwide spread, from December 2019, of the respiratory disease that has been named Coronavirus Disease 2019 (COVID-19), caused by a new coronavirus structurally related to the virus that causes severe acute respiratory syndrome (SARS), was the last major challenge and threat to public health (Fauci et al., 2020; Wu and McGoogan, 2020), and also had a great impact in the hematological setting (Willan et al., 2020). Furthermore, it has been observed that patients affected by a neoplastic disease who contract COVID-19 infection have a higher incidence of serious clinical complications (Intensive Care Unit admission, need of assisted ventilation, death) as compared to patients without neoplasia (Liang et al., 2020).

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1.1. Clinical management of hematologic patients in hospital and outpatient settings

As regards cytotoxic chemotherapy and all the other antineoplastic treatments currently administered to patients with hematological diseases, it was necessary for each single disease, for each different clinical condition and in each individual patient to make an accurate balance of the risk-benefit ratio, considering on one hand the potential benefit of the treatment, and the consequent damage constituted by its suspension or deferral, and on the other hand the immunosuppressive effect of the treatment itself, and the consequent increased risk of contracting a potentially lethal COVID-19 infection. For curative and immediately life-saving chemotherapy, efforts have been made not to postpone it and to respect the appropriate timing and dose-intensity, while for non-curative or maintenance therapy it was often decided to delay the start of the treatments, lengthen the intervals between the cycles and replace parenteral therapies with oral treatments, in order to reduce the patient access to the outpatient clinics. In outpatient clinics, telemedicine was often used, whenever possible: many follow-up visits have been replaced by telephone or email contacts or even videoconferences. The difficulty in continuing the administration of therapies was exacerbated by the frequent absence of medical and nursing staff due to COVID-19 disease or quarantine. Moreover, the medical and nursing staff of the hematological divisions was often reduced, as it has been often necessary to temporarily displace them in other divisions dedicated to COVID-19 patients. All these circumstances have caused a temporary disruption of the daily clinical practice of the hematologic institutions.

For single hematologic diseases, specific recommendations have been developed by national or international scientific societies.

The clinical management of patients with acute leukemia, myeloid (AML) or lymphoid (ALL) have been the subject of specific practical guidelines by the European Society for Blood and Marrow Transplantation (Brissot et al., 2020) and also by a panel of international experts (Zeidan et al., 2020); these patients, who frequently show a severe humoral and cellular immune deficiency, often require intensive chemotherapy, with a consequent high risk of Intensive Care Unit (ICU) admission and mortality. The purpose of these recommendations was to reduce these risks as much as possible, without compromising the effectiveness of the treatment. First of all, a screen for COVID-19 by PCR and high resolution thoracic computerized tomography scan was recommended in all newly diagnosed patients and in any case before starting each course of chemotherapy. As regards patients enrolled in clinical trials with innovative and potentially highly beneficial treatments, the continuation of the treatments was recommended as much as possible, reducing the outpatient face-to-face visits whenever possible and resorting to telemedicine (telephone or video consultations), home-delivery services and local blood tests.

As for AML, in patients fit to receive intensive therapy, while it was suggested not to modify the standard induction chemotherapy, it was recommended to reduce the intensity of cytarabine dose by 50% in consolidation therapy, and to use G-CSF to reduce the duration of neutropenia. However, in case of COVID-19 disease, the use of G-CSF should be carefully evaluated, given the potential risk of worsening the pulmoonary complications related to COVID-19. It was also suggested to consider maintenance therapy with hypomethylating agents as an alternative to intensive post-remission therapy in selected cases. For patients unfit for intensive treatment, low-dose treatment (hypomethylating agents or low-dose cytarabine, with or without venetoclax or targeted inhibitors) were recommended. For ALL patients, the use of glucocorticoids during the prophase, induction and consolidation was not changed, considering also their potential utility in reducing the immunopathological damage associated with COVID-19 infection, recommending an appropriate anti-infectious prophylaxis to prevent bacterial and fungal infections. However, in older patients (>65yrs) a reduction of steroid exposure was suggested, due to their immunosuppressive effect. A careful monitoring during asparaginase therapy was recommended, considering the risk of thrombotic complications associated with this drug, which could accentuate the thrombotic risk associated with COVID-19. As for allogeneic hematopoietic cell transplantation (allo-HCT), following the specific recommentations of the European Society for Blood and Marrow Transplantation (EBMT) (Ljungman et al., 2020), it was recommended to defer non urgent transplantations as much as possible, and to preferentially select patients at high risk of disease progression without allo-HCT, while it was suggested to avoid patients with more controversial indication for transplantation (e.g. refractory disease, high risk of non-relapse mortality).

Also for lymphomas, chronic lymphocytic leukemia and myeloma, specific recommendations have been developed, following the same general criteria used for acute leukemias (Di Ciaccio et al., 2020). For diffuse large B-cell lymphoma and high-grade B non Hodgkin lymphoma, it was recommended not to postpone therapy, and to maintain dose intensity and timeliness, while considering reducing the number of cycles of therapy in patients with less aggressive disease and favorable response to treatment (PET negativity after 4 cycles). In case of need for consolidation radiotherapy, it has been suggested to consider hypofractionation of consolidation radiotherapy, following the International Lymphoma Radiation Oncology Group (ILROG) Emergency Guidelines (Yahalom et al., 2020), with the aim of increasing the dose per fraction while reducing the number of daily treatments. This recommendation to administer radiation therapy, when necessary, using these alternative radiation treatment schemes was extended to all other hematological malignancies. Autologous stem-cell transplant (ASCT) was selectively recommended in patients where chemosensivity is demonstrated, avoiding prolonged delays of more than 2 months. For low-grade non Hodgkin lymphomas, it was first recommended to consider the delay of planned initiation of therapy where possible, or to consider a low-dose radiotherapy as a temporary palliative solution. For patients with follicular lymphoma who require treatment, R–CVP or R–CHOP regimens are preferred to bendamustine-based regimens, due to the risks of delayed infection with the latter. A maintenance immunotherapy with rituximab was not recommended, due to the possible increase in infectious risk.

In patients with classical Hodgkin lymphoma, no variations were suggested with respect to local treatment practices, although it was recommended to consider, in each patient, therapeutic choices that can reduce toxicity without compromising the effectiveness of the treatment. It was pointed out that symptoms of pulmonary toxicity due to some treatments (bleomycin, checkpoint inhibitors and radiotherapy) may mimic those of COVID-19 disease. Also for patients with chronic lymphocytic leukemia (CLL) (Di Ciaccio et al., 2020; Koffman et al., 2020), similarly to low grade lymphomas, a delay, where possible, of the planned initiation of therapy was

recommended, as many patients are basically immunocompromised and often present additional risk factors (advanced age, comorbidities). It was also suggested to choose oral therapies if accessible, and to reduce the dose and the duration of therapy in patients at lower risk, if disease control is achieved. For novel agents such as ibrutinib and venetoclax, special attention was recommended, as for both drugs an increased risk of pulmonary infections was reported, and temporary discontinuation of these agents in case of COVID-19 infection was suggested. However, as regards ibrutinib, an international survey by CLL experts claimed that the indications are controversial, and that its immunosuppressive effect must be balanced with its theoretical benefit in blunting the hyperinflammatory stage of COVID-19 disease (Koffman et al., 2020).

Patients with multiple myeloma (MM) have a compromised immune system, due to both the disease and anti-myeloma therapies, and a cohort study from five academic Centers in New York City of 100 patients with MM and COVID-19 infection reported case fatality rates in the higher range of reports from the general population (Hultcrantz et al., 2020). *T*herefore specific recommendations have also been drawn up for patients with MM (Di Ciaccio et al., 2020; Malard and Mohty, 2020). In general, also for MM patients a therapeutic choice based on an accurate risk assessment was recommended, considering the need for an optimal disease control in higher-risk patients while avoiding unnecessary treatment-related immunosuppression in lower-risk subjects. For patients who require treatment, preferential choice of oral agents was recommended: thalidomide, lenalidomide and pomalidomide as immunomodulatory drugs, oral rather than intravenous cyclophosphamide, and ixazomib as oral proteasome inhibitor (or alternatively home or self-administration of subcutaneous bortezomib). Moreover it was also suggested to reduce the use of dexamethasone as much as possible. For transplant-elegible patients, timely start of ASCT without delay, whenever possible, was recommended, possibly using outpatient stem-cell mobilization with only GCSF (+/− plerixafor).

Also patients with chronic myeloid neoplasm (Myeloproliferative neoplasm, MPN, and myelodysplastic syndromes, MDS) were also subject to special consideration by a panel of international experts (Zeidan et al., 2020). For chronic myeloid leukemia (CML) patients, no change in the management of tyrosine kinase inhibitors nor discontinuation of clinical trials was recommended, while it was recommended to extend interval between visits and to resort to mobile laboratory blood draws where available. Also for patients with Philadelphia-negative MPN, it was not suggested to modify the current cytoreductive treatment with hydroxycarbamide, anagrelide, interferon alfa or ruxolitinib, and above all it was recommended to avoid stopping ruxolitinib, because this drug may help to prevent possible immune cytokine release syndrome due to COVID-19 disease. Continuation of aspirin for thromboprophylaxis in patients with high thrombotic risk was also recommended, and it was also suggested to consider the switch from oral anticoagulation to low-molecular-weight heparin in case of acute COVID-19 disease.

The clinical management of patients with MDS should be based on an accurate risk assessment according to the revised international prognostic scoring system (IPSS-R) (Greenberg et al., 2012), also considering that a large proportion of these subjects are elderly and often show one or more comorbidities. For higher-risk MDS patients, a timely start of treatment with hypomethylating agents was recommended in patients with clinical significant cytopenia, while a close observation was suggested in subjects with only modest cytopenias; while it was advised to maintain normal intervals between cycles of therapy until patients respond to hypomethylating treatment, once the response was obtained it was recommended to consider lengthening the intervals between cycles, avoiding however a delay of more than 6 weeks. For lower-risk MDS patients, a watch-and-wait approach was generally suggested. However, the use of treatments capable of reducing the transfusion requirement, such as erythropoiesis-stimulating agents (ESAs) and luspatercept was recommended, while it was suggested to delay the start of lenalidomide in newly diagnosed patients with del(5q), due to its myelosuppressive effect.

Specific considerations have been made for patients with overlap syndromes (MDS/MPN), especially for patients with proliferative chronic myelomonocytic leukemia (CMML) (Patnaik et al., 2020). In these patients, who often show a mild-to-moderate leukocytosis, in case of COVID-19 infection there is a significant risk of leukemoid reactions, cytokine release syndrome and severe acute respiratory distress syndrome, and therefore a careful lowering of white blood cell count with hydroxycarbamide was recommended in case of extreme leukocytosis, even in asymptomatic patients.

A special consideration has been reserved for patients candidates to receive an autologous or allogeneic hematopoietic cell transplantation (HCT) or CAR T therapy, and also for these patients, practical guidelines have been published by the Infectious Diseases Working Party on behalf of the European Society for Blood and Marrow Transplantation (EBMT) *(*Ljungman et al., 2020*)*. First of all, before starting the transplant procedure, the availability of ICU beds, ventilators and of the stem cell product must be ascertained. It was however recommended to postpone non-urgent transplants, especially for non-malignant disorders. While it is obviously considered mandatory to test all the patients for COVID-19 before starting the conditioning regimen, the decision on how much to defer the transplant candidate patients if they becomes infected with COVID-19 was considered controversial. Although in general a deferral of at least 3 months was considered advisable, in patients at higher risk of progression of the underlying disease, and in particular in patients waiting for CAR T-cell therapy, a possibly shorter delay was recommended, however at least of 14–21 days, and in any case until the patient becomes asymptomatic and has two negative virus PCR swabs taken at least 24 h apart. In case of close contact with a subject with COVID-19, a minimum delay of 14–21 days for all transplant procedure (PBSC mobilization, bone marrow harvest, conditioning treatment) was suggested. As regards donation procedures, as donor availability might be restricted for various reasons (donor infection or quarantine, logistical reasons) it was strongly recommended to have secured stem cell product access by freezing the product before the start of conditioning regimen, or alternatively to keep an alternative donor as a back-up. COVID-19 was detected in blood, although no case of transmission from donor to recipient neither of blood products nor of cell therapies was reported so far (Chang et al., 2020). If the donor becomes infected with COVID-19, a suspension of the donation of at least 3 months was recommended (except in particularly urgent cases), while in case of close contact with an infected individual, a deferral of at least 28 days was advised. Based on a single center experience (Kanellopoulos et al., 2020), it has been reported that a non-myeloablative conditioning regimen followed by post-transplant cyclophosphamide (PTCy) for graft versus host disease (GVHD) prophylaxis

could attenuate COVID-19 disease, as, in haplo-identical HCT, the PTCy is known to abrogate Cytokine Release Syndrome (CRS) (physiopathologically similar to CRS associated with COVID-19).

1.2. Blood and blood products use

The collection and administration of blood and blood products was largely affected by the COVID-19 outbreak. First of all, even though during the pandemic there was a reduction in blood donations and therefore in the availability of blood products due to the lockdown, the demand for blood products decreased due to the postponement of elective surgeries (Fan et al., 2020b). Furthermore, it was observed that most patients with mild COVID-19 disease do not require blood transfusions, while about a third of patients with severe COVID-19 disease admitted to intensive care units (ICUs) require transfusions, mainly of red cell concentrates, frequently due to severe gastrointestinal bleeding. A mucosal damage of the esophagus, duodenum, stomach and rectum, with COVID-19 positive staining, was demonstrated (Xiao et al., 2020). Although in subjects with both symptomatic and asymptomatic COVID-19 infection viral-19 genomes were only detected in a small minority of blood samples examined, RNAemia is not equivalent to infectiousness, and to date no cases of hematogenous viral transmission have been documented for COVID-19 (Corman et al., 2020). In Italy, one of the most affected countries by the pandemic, specific recommendations have been developed by the Italian National Blood Center (CNS) in order to guarantee the safety of blood collection and of administration of blood products (Franchini et al., 2020a). These recommendations included an accurate anamnestic and clinical evaluation of the donors, with the use of triage processes in order to avoid the possible spread of the virus in the waiting rooms, and moreover an involvement of the associations and federations of voluntary blood donors to inform their staff and donors about the epidemiology, symptoms and preventive measures regarding COVID-19 infection. Thanks to this educational action towards donors and their associations, there was a temporary reduction of only 10% of donations at the beginning of the lockdown (compensated by a simultaneous reduction in elective surgical activity), but a subsequent increase in donations, following the campaign of the CNS and Italian Government encouraging blood donations, was observed. An international survey, involving 12 centers worldwide, was recently conducted, in order to develop and promote best practices for conducting pre-transfusion testing and issuing blood products; the survey included 9 questions regarding collection, storage and utilization of blood products and the therapeutic use of convalescent plasma (CP) for infected patients. Interestingly, 75% of the respondent centers reported a decrease in overall blood components utilization, due to the effect of COVID-19 pandemic. CP was considered or used in 75% of the responding centers to treat infected patients (Yazer et al., 2020). A multicenter interventional single-arm trial with CP, involving a total of 46 patients, was recently completed in Italy (Franchini et al., 2020b).

1.3. Hematologic laboratory alterations

Several alterations of the hematological parameters have been reported in patients with COVID-19 disease, some of which are useful for diagnostic and prognostic purposes (Fan et al., 2020a; Li et al., 2020; Terpos et al., 2020; Zini et al., 2020). The most common hematologic alterations include lymphocytopenia, with the presence of atypical reactive and plasmacytoid lymphocytes, neutrophilia and thrombocytopenia. In the early phase, neutrophil absolute count is frequently increased, with several morphological abnormalities of cytoplasmic granulation and of nuclear shape, and frequent presence of immature granulocytes (myelocytes and metamyelocytes) (Salib and Teruya-Feldstein, 2020; Zini et al., 2020). Lymphocytopenia is also frequent, especially in patients with more severe disease. Interestlingly, the majority of patients with a low lymphocyte count also show the presence of a highly pleomorphic reactive lymphocyte population, which becomes more evident several days after the onset of symptoms, characterized by atypical lymphocytes, mainly of medium or large size with loosely condensed chromatin and moderate to deep basophilic cytoplasm; some of them show a plasmocytoid morphology with an eccentric nucleus. Some lymphoid cells have one or more nucleoli and might be mistaken for blast cells. The observation of plasmocytoid lymphocytes might support a provisional clinical diagnosis of COVID-19 disease (Foldes et al., 2020; Gerard et al., 2020; Weinberg et al., 2020). Thrombocytopenia is frequent in patients with COVID-19: it was observed in 20.7% of subjects in a large series of 1476 consecutive patients admitted to Wuhan Jinyntan Hospital (Yang et al., 2020), and was associated with an increased risk of in-hospital mortality: non-survivors had significantly lower nadir platelet count than survivors. The association of a low platelet count with a worse prognosis was confirmed by a meta-analysis involving 31 studies with 7613 participants (Jiang et al., 2020). The aetiology of thrombocytopenia in COVID-19 disease is likely multifactorial: it could be caused by platelet activation and aggregation, with consequent formation of microthrombi, following damage to lung tissues and pulmonary endothelial cells, resulting in increased platelet consumption. Moreover, COVID-19 infection might cause a direct damage of hematopoietic cells and bone marrow stromal cells, leading to hematopoietic dysfunction; also the cytokine storm might cause the destruction of marrow progenitor cells. Also an increased levels of antibodies and immune complexes may increase platelet destruction (Xu et al., 2020). Finally, it's important to be aware that thrombocytopenia, in the absence of other symptoms or clinical signs, may constitute the initial presentation of COVID-19 disease (Ahmed et al., 2020).

Also the alteration of several inflammation biomarkers (procalcitonin, ferritin C-reactive protein, interleukin-6) is useful for diagnostic and prognostic purposes: a marked increase of each of these parameters is associated with an increased risk of death (Terpos et al., 2020). A large retrospective study conducted on a population of 1449 hospitalized subjects with COVID-19 found that two admission covariates (advanced age and elevated baseline D-Dimer) and the dynamic changes of four co-variates (Δ fibrinogen; Δ platelets; Δ C-reactive protein; and Δ lactate dehydrogenase (LDH) correlated with an increased risk of death (Li et al., 2020). These data confirm the prognostic importance, beyond the role of thrombocytopenia and of inflammation biomarkers, also of coagulation alterations. Coagulation disorders are frequent among COVID-19 patients, especially in subjects with more severe disease. An elevated D-Dimer is detected in almost 60% of severe cases, most of which fulfill the diagnostic criteria for disseminated intravascular

coagulation (DIC), and is associated with an increased risk of Acute Respiratory Distress Syndrome (ARDS) and death (Guan et al., 2020; Tang et al., 2020; Terpos et al., 2020). The risk of venous thromboembolism (VTE) in COVID-19 hospitalized patients is an important issue, likely due to several aetiological factors: endothelial cell activation/damage caused by the virus binding to ACE2 receptors, acute inflammatory condition with release of large amounts of cytokines, prolonged immobilization, dehydration, mechanical ventilation, central venous catheterization, along with other pre-existing cardiovascular risk factors. Therefore an accurate clinical laboratory and instrumental diagnostic evaluation is mandatory, not only in COVID-19 patients admitted to hospital, but also in asymptomatic or outpatient patients, and the start of antithrombotic prophylaxis is recommended in COVID-19 patients with thrombotic risk (whatever hospitalized or outpatients), preferentially using low molecular weight heparins (LMWH) or unfractionated heparin (UFH). Specific recommendations have been published by the International Society of Thrombosis and Haemostasis (ISTH) regarding recognition and management of coagulopathy in COVID-19 patients (Thachil et al., 2020); based on the currently available literature, the detemination of D-Dimers, prothrombin time and platelet count was recommended in all patients with COVID-19 infection. In addition to these parameters, the measurement of fibrinogen level was also recommended for monitoring the evolution of coagulopathy, and the administration of LMWH (which has also been shown to have anti-inflammatory properties) was recommended in all patients, including those non critically ill. Specifical guidelines have also been published by the Scientifc and Standardization Committee on the diagnosis, prevention and therapy of venous thromboembolism in COVID-19 hospitalized patients (Spyropoulos et al., 2020).

Declaration of competing interest

All the authors declare no conflict of interest.

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