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Opinion

The CoV-2 outbreak: how hematologists could help to fight Covid-19

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ABSTRACT

COVID-19 is a medical emergency, with 20 % of patients presenting with severe clinical manifestations. From the pathogenetic point of view, COVID-19 mimics two other well-known diseases characterized by cytokine storm and hyper-activation of the immune response, with consequent organ damage: acute graft-versus-host disease (aGVHD) and macrophage activation syndrome (MAS). Hematologists are confident with these situations requiring a prompt therapeutic approach for switching off the uncontrolled cytokine release; here, we discuss pros and cons of drugs that are already employed in hematology in the light of their possible application in COVID-19. The most promising drugs might be: Ruxolitinib, a JAK1/2 inhibitor, with a rapid and powerful anti-cytokine effect, tyrosine kinase inhibitors (TKIs), with their good anti-inflammatory properties, and perhaps the anti-Cd26 antibody Beigelomab. We also present immunological data from gene expression experiments where TKIs resulted effective anti-inflammatory and pro-immune drugs. A possible combined treatment algorithm for COVID-19 is here proposed.

1. Introduction

Coronavirus disease 2019 (COVID-19), sustained by the new Coronavirus SARS-CoV-2, started in China in December 2019 in the province of Hubei and then rapidly overspread over the world, becoming a “pandemic”. The 22 April 2020, the European Centre for Disease Prevention and Control reported 2,520,522 infected subjects around the world, with 176,786 deaths [<https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>]; 1,101,681 people were infected in Europe and 825,041 in USA, with 107,453 and 45,063 deaths, in Europe and USA, respectively [<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>].

This great number of infected subjects is requiring an enormous worldwide effort for hospitalizing and caring all patients who have to receive firstly an adequate diagnostic approach (chest X-ray or CT, viral genome identification and quantitation, serology), then the best possible therapies that might avoid the more severe phase of disease. From the clinical point of view, the majority of patients remains asymptomatic or presents mild symptoms; Mizumoto et al. conducted an epidemiologic study on the 3711 people who remained on board of the Diamond Princess cruise ship, blocked in Japan after identification of a

SARS-CoV-2-positive passenger; these authors estimated that 17.9 % of all infected cases remained asymptomatic during quarantine [1]. Another group estimated that the rate of symptomatic cases was 101/10,000, after a median incubation time of 14 days [2]. Moreover, the Italian COVID-19 Surveillance Group, during the peak of infection, reported 460 deaths on 85,308 infected individuals (9.9 %), with an overall case-fatality rate around 7.2 %, substantially higher than in China (2.3 %), thus highlighting the compelling need for more effective approaches. The median age of infected subjects was 62 years, 85 % of deaths occurring in patients between 70 and 89 years. Moreover, only 1.2 % of infected patients presented at the hospitalization without comorbidities, while 23.5 % had one, 26.6 % two, and 48.6 % three or more comorbidities. The most frequent concomitant diseases resulted: previous ischemic heart attack or stroke, atrial fibrillation, hypertension, diabetes, dementia, a recent history of cancer, chronic liver disease or renal failure. Only 7.5 % of patients did not present any symptom at the hospital admission, 12.7 % were pauci-symptomatic, 37.9 % and 19.6 % manifested mild and severe symptoms, respectively, while 4.4 % were critical [<https://www.epicentro.iss.it/coronavirus/>]. In the international scenario, the most frequent clinical manifestations were fever and dyspnea, whilst cough, diarrhea and hemoptysis were

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less common; acute respiratory distress syndrome (ARDS) was observed in 96 % of severe cases, followed by acute renal failure in one third of them; super-infections were documented in 8.5 % of critical cases where septic shock and the macrophage activation syndrome (MAS) were the most frequent cause of death [3,4]. From the early stages of infection patients develop lymphopenia and neutrophilia; in the more advanced cases, lymphocyte further reduce, liver failure appears with hypoalbuminemia, and the hyper-inflammatory status, characterized by high levels of reactive protein C, ferritin, D-dimer, LDH, troponin and N-terminal fragment of the B-type natriuretic peptide (NT-proBNP), is demonstrable [5,6].

The pathogenesis of this “hyper-inflammation” have been recently revised: chemokines, such as MCP-1, IL2, IL-7, IL-10, G-CSF, IP-10, MIP-1A and IL6 are highly expressed, whereas TNF-alpha seems to be only moderately up-regulated. Cytotoxic CD8+ and exhausted T cells, together with an abnormal balance between Th1 and Th2 lymphocytes, mirror the onset of a severe immune dysfunction [7]. Consequently, several approaches able to switch off inflammation by maintaining at the same time the host’s antiviral immunocompetence have been rapidly designed and tempted: **Chloroquine**, already employed in rheumatological diseases, inhibiting the attack of the SARS-CoV-2 to the ACE2 receptors (that represent one of the two virus receptors) resulted quite effective [8], alone or in combination with azithromycin [9]. **Tocilizumab**, an anti-IL6 antibody, already used both in rheumatoid arthritis [10,11] and in the cytokines release syndrome after infusion of CAR-T in patients affected by acute lymphoblastic leukemia or aggressive lymphomas [12,13], has been employed with success in COVID-19. Recently, an Italian group proposed a new treatment algorithm whose backbone is represented by Chloroquine; Tocilizumab is used precociously in all patients with high levels of IL6 and D-dimer, including those, especially the elderly cases, with hypoxemia without severe dyspnea [14]. Other possible options from the “rheumatological” background are the anti-IL1 monoclonal antibody **Anakinra**, already effective in the MAS [15], and the JAK1/2 inhibitors, such as **Baricitinib**, already employed in rheumatoid arthritis [16], used alone or in combination with intravenous Immunoglobulins [14]. In 22 April 2020 a clinical trial aimed to assess the Baricitinib effectiveness in severe COVID-19 has been authorized by the Italian Drug Agency (AIFA) [<https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19>]. Finally, anti-TNF alpha antibodies, such as **Adalimumab**, prescribed for the treatment of psoriasis [17] and Behcet’s disease [18], have been proposed as possible further therapeutic tools for COVID-19 pandemic [7].

In this apocalyptic scenario, some authors already observed that this “rheumatological” approach, notwithstanding a clear fast and positive anti-inflammatory effect, could impair the immunological control of neoplasms in patients receiving chemotherapy or immunotherapy for cancer. Indeed, cancer patients showed a higher rate of severe events after SARS-CoV-2 infection in comparison with patients without cancer (39 % vs 8%) [19]. This epidemiological observation, in addition to the consideration that the majority of reported comorbidities in patients with critical COVID-19 were diseases characterized by a pro-inflammatory profile, underlines once again the need of identifying further drugs exerting a significant anti-inflammatory action but without losing their anti-tumor effect. On the basis of these considerations, we decided to review literature and what hematologists know about the relationship between hematological drugs, inflammation and immunity, in order to help the scientific community to definitively fight the COVID-19.

2. COVID-19 challenge: what hematologists learnt from hematological diseases

2.1. Two good “hematological” COVID-19-like models: the graft-versus-host disease and the MAS

In hematology, we have a well-known similar condition that mimics

the hyper-inflammation caused by the new Coronavirus: the **graft-versus-host disease**, in its acute (aGVHD) and chronic forms (cGVHD). GVHD, which interests about half of transplanted patients, can appear by or after 100 days from the allogeneic stem cell infusion, with a prevalence that ranges from 35 % to 55 %, according to donor type, conditioning regimen, disease status at transplant and prophylactic approach [20,21]. GVHD is the consequence of a misleading attack by donor T lymphocytes of several recipient’s antigens recognized as outsiders, with consequent damage of his/her liver, lungs, gastrointestinal tract, eyes, vagina, muscles and joints. Allogeneic T and B lymphocytes sustain this hyper-inflammation that causes tissue damage and fibrosis, both by increasing production of inflammatory cytokines (IL-1, IL-2R, IL-6, TNF alpha) and by the deposition of immune complexes. The intestinal epithelium damage releases bacteria and modifies the gut microbiome, further increasing the immune response: T CD8+ lymphocytes are especially activated by the recipient hematopoietic antigen-presenting cells (APC), whereas donor T CD4+ cells can be activated by other APC types, principally in the gut. The participation of other immunocompetent cells, such as NK, macrophages, monocytes and neutrophils, makes GVHD a hyper-inflammatory dangerous condition that well recapitulates what occurs in COVID-19, where the rapid Coronavirus replication impairs the IFN-induced immune response, with rapid increase of M1-oriented macrophages and pro-inflammatory cytokines [7]. Moreover, clinical manifestations, especially of the aGVHD, are similar to those observed in COVID-19: skin rash, diarrhea, elevated bilirubin, infections, pulmonary leak syndrome, eye and mouth damage and, in the chronic form, also fasciitis, myositis and fibrosis that mimic the systemic scleroderma [22,23].

Another COVID-19-like condition that hematologists and rheumatologists have to deal with is the Macrophage activation syndrome (MAS), an acute hyper-inflammatory condition characterized by activation and expansion of T cells and hemophagocytic macrophages, with the consequent cytokine storm, with increased levels of pro-inflammatory cytokines, such as IL-1, IL-6, IL-18, TNF alpha, and IFN gamma [24]. MAS is reported to interest about 4% of patients with juvenile idiopathic arthritis and systemic lupus erythematosus, but it can also represent a complication of hematological neoplasms or infections, with a mortality higher than 40 %, that makes MAS a real medical emergency [25]. From the diagnostic point of view, MAS is a febrile condition characterized by hyperferritinemia, multilineage cytopenia, coagulopathy, transaminitis, high levels of triglycerides, hypofibrinogenemia and splenomegaly. Classically, MAS is treated with high steroid doses and etoposide [26], but in the era of new biological drugs promising results derived from the use of anti-IL1 and anti-IL6 antibodies, like Anakinra, Canakinumab, Riloncept and Tocilizumab [27].

3. The hematological approach to COVID-19: pros and cons

Hematologists are already confident with GVHD and MAS, that require a rapid intervention for switching off the cytokine storm and controlling the exaggerated immune response. In the following, we’ll discuss positive and negative aspects of drugs employed for treating GVHD and MAS, in the light of their possible employ in the COVID-19 war.

3.1. Immunosuppressive agents

In aGVHD, treatment includes topic or systemic corticosteroids, anti-thymocyte immunoglobulins, cyclosporine, mycophenolate mofetil for appropriate management of acute phase. Novel approaches also include mesenchymal stem cells, etanercept and infliximab (anti-TNF alpha), daclizumab (anti-IL2) or vedolizumab (anti-a4b7), but results are still very preliminary and not worth to be considered for translating the experience deriving from the aGVHD “new era” directly to the COVID-19 [28]. About cGVHD as “inspiring source”, also in this case the first

line approach is represented by immunosuppressive agents [29] that seems to be *not really effective in COVID-19* [7].

3.2. Monoclonal antibodies

Tocilizumab, anti-IL6 monoclonal antibody, has been used also for treating aGVHD, with 70 % of partial remissions (PR). Nevertheless, in a series of 11 patients, 2 developed a bacterial sepsis, one of whom died [30]. Until today, 23 trials have been registered in the “clinical trials.gov” website, *thus supporting the promising use of this drug in COVID-19*. **Rituximab** has been also used as therapeutic tool in GVHD, with 60 % of overall response rate (ORR); however, as reported by the Italian cooperative group (GITMO), 3/38 treated patients died for infections [31], and in a meta-analysis involving 111 cGVHD patients, one third of them presented pneumonitis and Herpes virus reactivation [32]. No studies involving this monoclonal antibody have still registered in the “clinical trials.gov” website. *In our opinion, the use of Rituximab in the COVID19 could be not considered, either for the high rate of infections reported in the hematological context, or because Rituximab requires a too long time to be efficacious.*

Beigelimab, a monoclonal anti-CD26 antibody, has been recently reported to be efficacious in treatment of 69 steroid-refractory aGVHD patients. In the compassionate use, Beigelimab was administered at 3 mg/m²/day for 5 days, followed by six additional doses of 3 mg/m² at day +10, +14, +17, +21, and +24. The overall response rate at one month was 75 % in the prospective studies and 61 % in the compassionate use, with complete response rates of 11 and 12 %, respectively. Response in grade-III GVHD was higher than 70 %, and response in grade-IV GVHD cases about 60 %, with higher response rates described for skin, liver, and gut. The tolerability of treatment was good, with the most common adverse events being diarrhea, cytomegalovirus reactivation, infections, probably more linked to the GVHD and the previous steroid treatment than to the antibody itself. In the 8 complete responders there was only one late death due to infections; in the 38 partial responders, the infection rate was 10.5 % [33]. Recently, the DPP4/CD26 glycoprotein has been reported to be one of the two receptors for the spike S1 SARS-CoV2 surface protein, together with the angiotensin converting enzyme (ACE2) [34]. Once activated by SARS-CoV-2, this protease helps virus 1) to reduce autophagy, the process physiologically aimed to eliminate external microorganisms from the host cells, 2) to sustain the hyper-inflammatory status and 3) to reduce the host anti-viral immune response [35]. The hypothesis of destroying this strict link by the anti-CD26 antibodies or the DPP4 inhibitors, already employed in the diabetic patients, seems really interesting [36]. DPP4 inhibitors have been already demonstrated to be efficacious in several *in vitro* models of SARS [34] and, considering the 80 % of homology between old and new Coronavirus, DPP4 inhibitors might be useful also in the COVID-19 pandemic [37]. Nevertheless, no studies with Beigelimab have still been registered in the “clinical trials.gov” website. *Considering these novel findings about the possibility of destroying the CD26 axis connecting Coronavirus and inflammation/perturbed host immunity, in our opinion, the use of Beigelimab, probably for a short time course, might be considered an interesting approach, worth to be tested in the COVID19.*

3.3. BTK inhibitors

In the last two years, FDA and EMA licensed Ibrutinib as treatment for steroid-refractory cGVHD. **Ibrutinib**, already effective in high risk chronic lymphocytic leukemia (CLL) [34], in addition to the Bruton Kinase, also inhibits another kinase, the interleukin-2-inducible T-cell kinase (ITK), that is involved in the selective activation of T-cells that drive immune reactivity toward healthy tissues [38], and a SRC kinase, HCK, whose over-expression, in a murine model, has been reported to be responsible for extensive pulmonary inflammation and enhanced immune response, particularly in older

mice [39]. In cGVHD, Ibrutinib, switching off the cytokine storm, was successful in two third of cases, with 21 % of complete and 45 % of partial responses [40], with a significant improvement of patients' quality of life [41]. Unfortunately, this treatment is characterized by adverse events that cause treatment discontinuation in 30 % of patients; in particular, pneumonitis, fatigue and diarrhea of grade ≥ 3 occur in 71 % of patients in the first year and in 25 % in the second year, inducing therapy discontinuation in 40 % of cases [38]. In agreement with these results, the experience in CLL reported high infection rates: in a cohort of 378 patients, serious infections were observed in 11.4 % of cases, especially bacterial and fungal [42]. At the moment, no clinical trials using Ibrutinib in COVID-19 have been registered in the “clinical trials.gov” website; nevertheless, Treon and coworkers in the last days published in Blood an interesting report concerning the low rate of COVID-19 occurrence in patients with Waldenstrom's macroglobulinemia (only 6 out of 300 individuals). All patients experienced cough and fever as prodromal symptoms; the 5 patients on Ibrutinib 420 mg/day experienced no dyspnea and did not require hospitalization, with a shorter disease course in comparison with the one patient receiving lower Ibrutinib dose, who, on the contrary, required the administration of Tocilizumab and i.v. immunoglobulins [43].

In our opinion, Ibrutinib, might be a potential candidate for fighting the CoV-2, but probably if used for a short time, due to the high number of infections and treatment discontinuations that usually characterize its use in the hematological scenario. Clinical trials are needed to conclude if the balance weighs more on the side of efficacy or toxicity.

3.4. JAK2 inhibitors

The other drug licensed by FDA and EMA for treatment of GVHD is **Ruxolitinib**, already successfully employed for reducing spleen dimension and improving quality of life and survival of patients affected by myelofibrosis [44]. Ruxolitinib, a JAK1/2-inhibitor, decreases the activity of Th1 lymphocytes, and, through modulation of the STAT pathway, the secretion of pro-inflammatory cytokines, such as TNF alpha, IL1, IL6, and IFN gamma [45]. Ruxolitinib is effective both in acute and in chronic GVHD: in 71 cases of steroid-refractory aGVHD, Ruxolitinib offered 55 % of ORR and 27 % of CR, especially in skin, gastrointestinal tract, and liver. Median duration of response was 345 days and the overall survival (OS) at 6 months 51.0 %. Cytopenias occurred in half of cases, peripheral edema in 45 %, but no significant infective toxicity has been reported [46]. In another cohort, Ruxolitinib, at a dose of 20 mg/day, offered 57.1 % of ORR; reported adverse events were anemia, thrombocytopenia, neutropenia, infections, edema, bleeding, and transaminitis [47]. In the cGVHD, Ruxolitinib has been reported to be effective in 80 % of patients; nevertheless, reactivation of CMV occurred in 15 % of patients [48]. In a meta-analysis including 414 patients with cGVHD, during treatment with Ruxolitinib infections occurred in 20 % of patients, more frequently sustained by bacteria (55 %) and CMV (39 %) [49]. The pro-infective aspect of Ruxolitinib is also evident in myelofibrosis, where cases of hepatitis B [50] and tuberculosis (in 1.4 % of cases) [51] reactivation, in addition to pneumonitis sustained by *Pneumocystis jiroveci* [52], have been reported. In the last weeks, 8 clinical trials with Ruxolitinib in COVID-19 started, with dose ranging from 10 to 20 mg/day. The first 11 cases treated in Italy avoided the incoming intubation, so confirming in the real life the anti-inflammatory power of this JAK1/2 inhibitor.

In our opinion, Ruxolitinib could represent a very good candidate against COVID-19 for its well-known powerful and fast anti-inflammatory effect; nevertheless, the high rate of viral and microbial reactivation observed in the hematological setting might represent a caveat in its prolonged use in the COVID-19.

3.5. Tyrosine kinase inhibitors

Another class of drugs already employed in the treatment of GVHD that could help to win the COVID-19 challenge are the tyrosine kinase inhibitors (TKIs), already successfully employed in treatment of chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia and stromal gastro-intestinal tumor (GIST) [53]. Imatinib has been the first TKI licensed for CML treatment, followed by Nilotinib, Dasatinib, Bosutinib (second generation TKIs) and Ponatinib (third generation TKI). All TKIs, and especially those of second and third generation, in CML offer high rates of complete hematological, cytogenetic and molecular responses [53], necessary key for treatment discontinuation (TFR), that has success in about 40 % of patients [54]. Different studies focused on TFR explored the impact of TKIs on the immunological response, showing that this class of drugs play a positive effect on NK cells whose number and activated status is fundamental for maintaining deep molecular response without treatment [55,56]. Moreover, TKIs are able to restore the immunocompromised status observed in CML patients at diagnosis by reducing myeloid-derived suppressor cells, re-activating T and NK cells, and reducing the expression of PD-1 on T and NK lymphocytes and of PD-L1 on the microenvironment and on neoplastic clone [57]. **Imatinib** has been employed with success also in GVHD, but mainly in its chronic form, where it was successful in about 60 % of cases [58]. From the safety point of view, in a series of 19 cases only one pneumonitis and one CNS infection by JCV have been reported [59]. In another cohort with sclerodermic GVHD Imatinib was compared to Dasatinib: one of the 4 patients receiving Imatinib had pneumonitis versus 2 of the 5 cases treated with Dasatinib [60]. Two trials proposing Imatinib in COVID-19 have been already registered in the “clinical trials.gov” website (NCT04357613, NCT04356495), both involving elderly patients. In a third study, Imatinib will be compared to hydroxicloroquine, Lopinavir/ritonavir, and Baricitinib (NCT04346147).

In our opinion, Imatinib might represent a good therapeutic possibility in the COVID-19 for its demonstrated anti-inflammatory activity added to a good safety profile, but a caveat has to be done about the delayed onset of its positive therapeutic effects.

Dasatinib has not been further used in GVHD, but the toxicities that it causes in CML might contraindicate its use in the COVID-19. In fact, about 25 % of CML patients develop pleural effusion during Dasatinib treatment [61]. Several mechanisms have been explored, from the inhibition of PDGFR beta to increased T lymphocytes in pleural fluid [62]. In multivariate analysis, a previous skin rash or history of autoimmune disease resulted as significant factors predicting pleural effusion [63]. About infective risk during Dasatinib administration, the incidence of grade 3/4 infections resulted 11 % [64]; in the DASISION trial, which compared Dasatinib with Imatinib as first-line treatment, 4.5 % of patients in the Dasatinib and less than 1% in the Imatinib cohort died for infections, so sustaining the high infective risk of Dasatinib in comparison to Imatinib [65]. At the moment, no studies with Dasatinib in COVID-19 have been registered in the “clinical trials.gov” website. On the basis of available data, *in our opinion, Dasatinib might be not a valid candidate for the COVID-19 treatment.*

On the contrary, different promising suggestions come from some *in vitro* and *in vivo* models that would support the use of **Bosutinib** as a powerful anti-inflammatory agent. This TKI is today indicated for treatment of CML Imatinib-intolerant or resistant patients [66]. Differing from Dasatinib, whose pro-inflammatory action is supported by the high rate of pleural effusion, Bosutinib resolved this adverse event in 17/20 cases presenting effusion during treatment with Dasatinib. Moreover, the safety of Bosutinib from the immunological point of view is supported by the quite total absence of infective adverse events [67]. Moreover, in a model of membranous glomerulonephritis, Bosutinib was able to ameliorate renal damage by reducing expression of IL2R, IL4R, and by inhibiting JAK2/JAK3 (that sustain the inflammatory

pathway) [68]. In another murine model of intra-cerebral hemorrhage with brain injury caused by post-bleeding inflammation, Bosutinib once more showed its anti-inflammatory action: inhibiting SIK-2, it activates CREB and I κ B, so blocking the NF- κ B-derived inflammation. Moreover, Bosutinib shifted the macrophagic response from M1 to M2, and decreased pro-inflammatory cytokines production [69]. Bosutinib and Nilotinib were also used and compared in a murine model of Alzheimer's disease (where brain plaques are considered a consequence of hyper-inflammation). In this context, both TKIs decreased inflammation by reducing TNF alpha, IL4, IL6, IL3, and IL2 levels and increasing IL10 and CX3CL1, but, in comparison with Nilotinib, Bosutinib increased IL-10 and CX3CL1 also in the peripheral blood [70]. Thus, the anti-inflammatory profile of Bosutinib is evident. About its safety, in the BEFORE trial, where Bosutinib and Imatinib were compared in 536 CML patients in first line, grade 3/4 infection rate was 3.4 % in the Bosutinib versus 4.9 % in the Imatinib arm, with only 0.4 % of upper respiratory tract infections in the cohort treated with Bosutinib [71]. All these data suggest that Bosutinib might have a relevant anti-inflammatory effect, with a good safety profile; at the moment, no studies with Bosutinib have been registered in the “clinical trials.gov” website. *Nevertheless, in our opinion, Bosutinib could be considered a possible effective drug in the COVID-19. Nevertheless, no experience with this drug has been done in GVHD or MAS.*

Nilotinib is a valid second-generation TKI approved for treatment of CML in first or subsequent lines [72]. Nilotinib is now in experimentation also in GVHD, on the basis of data from the preclinical studies that clearly demonstrated its anti-inflammatory power. Indeed, Nilotinib significantly reduced production of pro-inflammatory cytokines (IL-2, IFN-gamma, TNF alpha, IL-17, TGF beta), without losing the lymphocyte immunocompetence [73,74]. Nevertheless, no definitive data on Nilotinib safety in GVHD are still available; consequently, safety profile must be derived from the experience in CML. In the EN-ESTnd trial, comparing Nilotinib and Imatinib in 564 CML patients in first line, all grade infection rate was 17 % in the Nilotinib versus 14 % in the Imatinib arm, with grade 3/4 infections rate in the Nilotinib cohort less than 1% [75]. In conclusion, Nilotinib seems to be an anti-inflammatory agent with a good infective safe profile; these features could make it, in our opinion, a good candidate in the COVID-19 setting; nevertheless, we have to consider its high rate of cardiovascular complications seen in CML [76,77] that could be the consequence of the inflammatory endothelial damage, as shown by higher IL6 and lower IL10 levels in CML patients presenting cardiovascular events [78]. At the moment, no studies with Nilotinib in COVID-19 have been registered in the “clinical trials.gov” website. *In our opinion, this pro-atherogenic aspect might made Nilotinib a sub-optimal candidate in the COVID-19 context.*

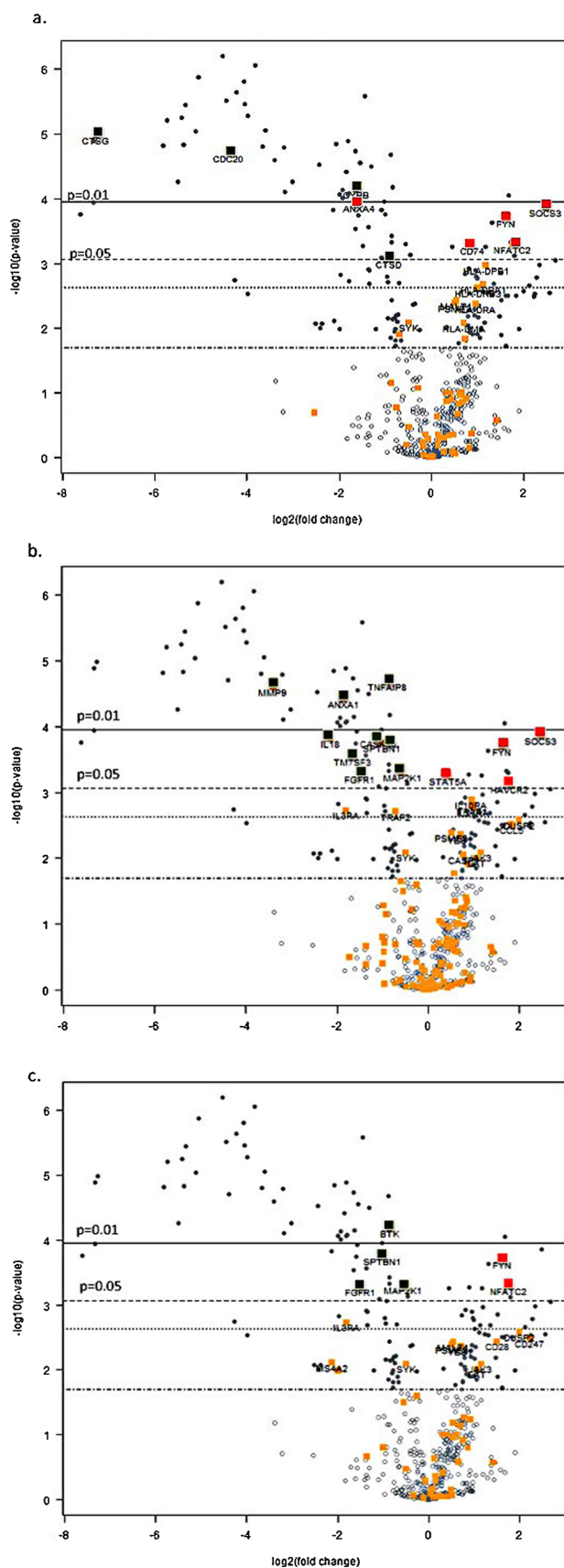
3.6. Interferons

Interferons (IFNs) are old, but at the same time “evergreen” drugs, for many years used for treating different hematological diseases, from CML and Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) to lymphomas and myeloma, due to their potent immune enhancing capacity that allows recognition and elimination of neoplastic cells by the patient's immune system. In CML, Interferon has been used until the introduction of TKIs; its offered hematological and cytogenetical, but very few molecular responses. Nevertheless, for many years it represented an advantageous treatment in respect of hydroxyurea [79]. In MPNs, IFNs are still successfully employed, especially in younger people, where their discontinuation after long-term treatment may be followed by several years with normal cell counts and low-JAK2V617F burden, that once again supports the concept that IFN-alpha is able to modulate and enhance the immune system-mediated defense against cancer [80]. In lymphomas, IFN is still the first line of treatment of hairy cell leukemia [81] and, with less fortune, has been employed as maintenance therapy in indolent lymphomas, especially after

autologous transplantation [82]. In multiple myeloma, IFN has been demonstrated to reduce plasmacells growth by down-regulating the IL6 production, with a synergic action with melphalan and corticosteroids in reducing the monoclonal component. IFN has also been used as maintenance after autologous transplantation before introduction in the clinical practice of lenalidomide and bortezomib, but with doubt favorable prognostic impact [83]. Moving from the hematological context to the SARS, during the outbreak of 2002 IFNs were also tried; a meta-analysis including 54 studies with IFN was performed in 2006, with discordant results. Indeed, while the *in vitro* studies showed a good antiviral power of IFNs (with IFN beta being more effective than alpha), the *in vivo* studies were inconclusive, with a doubtful prognostic advantage in respect of steroids [84]. At the moment, 6 studies, aimed to understand if IFNs might be useful in COVID-19, have been registered in the “clinical trials.gov” website, trying either IFN alpha/beta or lambda (NCT04344600, NCT04350671, NCT04343768, NCT04343976, NCT04254874, NCT04320238). Interestingly, one of these studies is employing the IFN alpha via aerosol, probably in order to avoid the systemic adverse events (flu-like syndrome, fatigue, hypothyroidism, creatinine increase) that frequently lead to the drug discontinuation in the hematological patients [85]. The use of IFN lambda (type III IFN), seems interesting, based on different action mechanisms that characterize type I and III IFNs. Indeed, for decades, type I IFNs (IFN alpha and beta) have been explored as mediators of rapid, innate antiviral protection. In 2003, a novel group of three cytokines, now known as type III IFNs (IFN lambda), have been discovered. The distinctive actions of type I and type III IFNs depend on the engagement of different receptors: type I IFNs trigger pro-inflammatory responses via the recruitment and activation of immune cells, promoting an anti-viral state in the host, while type III IFNs signal is restricted to epithelial cells and neutrophils. Therefore, type III IFN administration as a prophylactic treatment or at an early stage of COVID-19 might result in a good antiviral response localized to epithelial cells, reducing side effects and inflammation associated with the systemic action of type I IFNs [86] *In our opinion, considering the actual availability of different clinical options, because of their poor tolerability, IFNs might be not good candidate in the COVID-19 therapy.*

4. Our personal contribution to the COVID-19 war: the analysis of the immune transcriptome

After this analysis, we became convinced that, in addition to Ruxolitinib, Imatinib and Bosutinib would represent possible interesting therapeutic tools in the COVID-19 war. Thus, we decided to contribute to the COVID-19 challenge by confirming *ex vivo* the anti-inflammatory power of Imatinib and if and how it could modify the immunological profile of our patients. Thus, we used the Nanostring technology (Nanostring, Seattle, USA) for analyzing the immune transcriptome profile of 5 patients affected by CML, at diagnosis and after 6 months of treatment with Imatinib. The tested RNAs have been already stocked in our laboratory as leftovers that the respective patients donated to us for further non-profit researches after routine diagnostics. We employed the “Human nCounter Myeloid Innate Immunity panel” that measures the expression value of 770 genes involved in 19 different pathways fundamental for the innate immune response. Results were analyzed by the nCounter Advanced Analysis 2.0 software. In Fig. 1 we represented some of the up- (red squares) and down-regulated (green squares) genes by volcano plots, and in the Table 1 are listed all down- (in green) or up- (in red) regulated genes and the pathways where they are involved. In Table 2 we better detailed all genes that resulted significantly deregulated after Imatinib, their respective physiological role and their possible contribution to inflammation and immunological infection control. Overall, 40 genes resulted down- and 18 up-regulated by Imatinib; 35 of these down-regulated genes may sustain the inflammation in different autoimmune diseases, whilst 5 are anti-inflammatory. After Imatinib-induced gene expression down-



(caption on next page)

Fig. 1. CML: Volcano plots of some pathways de-regulated by 6 months of treatment with Imatinib. Some of the up- (red squares) and down- (green squares) genes de-regulated during treatment of CML patients with Imatinib are represented by volcano plots. Statistical significance (at 0.05 and 0.01) are indicated with dotted and continuous lines, respectively. In a) the Antigen presentation pathway, in b) the Cytokines pathway, in c) the FCR signaling pathway is represented.

Table 1
CML gene expression profiling.

Gene Id	Pathway	Gene Id	Pathway
ANXA4	Ag present	GRN	pat resp
ARG1	metabolism	GSN	pat resp
BTK	BCR	IL18	cytokines
C3AR1	complement	ITGAM	migration
CAMP	pat respo	LTA4H	metabolism
CASP10	cytokines	MAP2K1	angiogenesis
CDC20	Ag present	MMP8	ECM
CEACAM1	migration	MMP9	ECM
CEACAM8	migration	MPO	pat resp
CLEC5A	ly activation	NECTIN1	migration
COL17A1	ECM	OLR1	migration
CTSG	Ag present	PGLYRP1	pat resp
CXCL2	chemokines	PLAU	complement
CXCL3	chemokines	PRG2	pat resp
CYBB	Ag present	PTX3	pat resp
DAGLB	metabolism	RNASE2	pat resp
ELANE	ECM	RNASE3	pat resp
EPX	pat resp	SPTBN1	cytokines
FGFR1	cytokines	TM7SF3	cytokines
FUT4	metabolism	TNFAIP8	cytokines

Gene Id	Pathway
CCL5	chemokines
CCR4	chemokines
CCR5	chemokines
CD28	migration
CD74	Ag presentation
CX3CR1	chemokines
CXCL16	chemokines
CXCR3	chemokines
FYN	Ag presentation
HAVCR2	cytokines
IFNG	Ag presentation
JAK3	chemokines
NFATC2	Ag presentation
PDE4A	metabolism
SERPINB9	pat resp
SOC3	Ag presentation
STAT5A	cytokines
TLR3	pat resp

Table represents all genes that, among the 770 genes whose expression had been tested by the Nanostring “Human nCounter Myeloid Innate Immunity” panel, resulted up- (in red) and down- (in green) regulated after 6 months of treatment with Imatinib. The adopted Nanostring panel allows to classify genes in 19 different pathways. The Table reports for each gene its respective pathway of belonging.

regulation, the final effect was a significant reduction of pro-inflammatory cytokines and chemokines mRNAs. Unfortunately, these data are not completed by the quantification of cytokines in the serum, because of the retrospective nature of the study. On the other hand, among the 18 genes those expressions increased after Imatinib, 15 support the physiological innate immune response. More in detail, among the down-regulated ones, we found some genes that are highly expressed in autoimmune diseases: ANXA4, high in the Sjogren’s syndrome [87], CASP10, high the Crohn’s disease [88], while CEACAM8 [89], CTSG [90], and IL18 [91] are overexpressed in arthritis. Moreover, CLEC5A, increased after neurogenic shock [92], CXCL2 and GRN are highly expressed in the Alzheimer’s disease [93,94], ITGAM was elevated in psoriasis [95], and PGLYRP1 had high levels in chronic

Table 2
CML gene expression profiling.

GENE ID	function	output on	ref
ANXA4	high in Sjogren	anti infl	[87]
ARG1	immunosuppressive	pro immun	[97]
BTK	sustains GVHD	anti infl	[38]
C3AR1	neutrophils chemotaxis antagonist	pro immun	[98]
CAMP	increased in inflammation	anti infl	[126]
CASP10	increased in Chron	anti infl	[88]
CDC20	increased in the adiposity inflamm model	anti infl	[127]
CEACAM1	inhibits T lynf	pro immun	[99]
CEACAM8	high in arthritis	anti infl	[89]
CLEC5A	high in neurogen shock	anti infl	[92]
COL17A1	induce IL7 that sustains T & B lynf	anti immun	[128]
CTSG	high in rheumatic arthritis	anti infl	[90]
CXCL2	high in Alzheimer	anti infl	[70]
CXCL3	sustain adipogenesis	anti infl	[129]
CYBB	increased in inflammation	anti infl	[130]
DAGLB	sustains production of arachidonic acid	anti infl	[131]
ELANE	high in LPS inflammation	anti infl	[132]
EPX	high in asthma	anti infl	[133]
FGFR1	high in prostatic inflammation	anti infl	[134]
FUT4	increased in bacterial infections	anti infl	[135]

GENE ID	function	output on	ref
GRN	high in dementia	anti	[94]
GSN	increases NK apoptosis	pro immun	[100]
IL18	high in arthritis	anti	[91]
ITGAM	high in psoriasis	anti	[95]
LTA4H	high after trauma	anti	[113]
MAP2K1	high in sinusitis	anti	[114]
MMP8	high in intra-amniotic infections	anti	[115]
MMP9	high in skin healing	anti	[116]
MPO	high in neutrophils	anti	[117]
NECTIN1	high in Chlamidial infection	pro imm	[101]
OLR1	NFkB activator	anti	[118]
PGLYRP1	high in gengivitis	anti	[96]
PLAU	high after thrombosis	anti	[119]
PRG2	eosinophils basic protein	anti	[120]
PTX3	increased by IL6	anti	[121]
RNASE2	high in inflamm, anti-viral	anti anti-imm	[125]
RNASE3	anti viral	anti imm	[125]
SPTBN1	reduces TGFb	pro	[122]
TM7SF3	reduces nitric oxid	pro	[123]
TNFAIP8	high in inflamm	anti	[124]

GENE ID	function	output on	ref
CCL5	activates NK	pro immun	[138]
CCR4	high in asthma	pro	[137]
CCR5	activates NK	pro immun	[136]
CD28	inactivated by PD1	pro immun	[139]
CD74	increases MCHII expression	pro immun	[140]
CX3CR1	high in antifungal resp	pro immun	[141]
CXCL16	high in anti-viral resp	pro-immun	[105]
CXCR3	high in T effector	pro immun	[142]
FYN	high in inflamm/sustains NK	pro pro imm	[143]
HAVCR2	high in anti-viral resp	pro-immun	[106]
IFNG	antiviral	pro immun	[107]
JAK3	shift from M1 to M2 resp	anti	[102]
NFATC2	increases T memory	pro immun	[144]
PDE4A	low in sepsis	anti	[145]
SERPINB9	activates CDS	pro immun	[146]
SOC3	low in arthritis	anti	[103]
STAT5A	high in colon inflamm	pro	[147]
TLR3	anti-viral/anti-inflamm	anti pro imm	[104]

Table represents all genes that resulted Up- (in red) and down- (in green) regulated after 6 months of treatment with Imatinib, as listed in Table 1. Table 2 in addition for each gene reports the respective physiological function (with correspondent literature references) and the final effect resulting from mRNA de-regulation made by 6 months of Imatinib, with focus on the inflammation and on the immunological infection control.

gingivitis [96]. All these genes were down-regulated by Imatinib, as a demonstration of its anti-inflammatory action. At the same time, the anti-inflammatory effect exerted by Imatinib was also sustained by the reduced expression of the genes that identified the mast cells (Fig. 2). Our Nanostring analysis also demonstrated that, while Imatinib reduced inflammation, the patient's immunocompetence was not lost. Indeed, Imatinib down-regulated several genes that physiologically impair the T- and NK-cell response, such as ARG1 [97], C3AR1 [98], CEACAM1 [99], GSN [100] and NECTIN1 [101]. On the contrary, this TKI up-regulated some genes that usually support the immune response, such as JAK3, able to switch the macrophagic response from M1 (pro-inflammatory) to M2 (anti-inflammatory) [102], SOCS3, which had a low expression in arthritis [103], while TLR3 displayed low levels in inflammation and during viral infections [104]. Interestingly, Imatinib on the other hand also increased expression of some genes relevant for the antiviral response: CXCL16 [105], HAVCR2 [106], IFNG [107], RNASE2 and RNASE3 [108,109]. Finally, during Imatinib treatment, an increase in T cytotoxic and activated NK cells has been observed (Fig. 2).

In conclusion, even if preliminary, our findings agree with data already published by Alves et al. that reported an increased number of NK cells and lower IL21 levels during treatment with TKIs and IFN [110], and support the hypothesis that Imatinib might be a very good candidate to fight COVID-19 due to its anti-inflammatory action in a context of a conserved and efficient immunological infection control (Fig. 3).

5. Conclusions

In Table 3 we resumed characteristics, pros and cons of drugs that, on the basis of above reported considerations, might be translated from the hematological scenario to the CoV-2 pandemic. Nevertheless, a

further consideration has to be done about the costs of these possible new treatments: in 2018, a group of researchers from the Mayo Clinic performed a cost/effectiveness analysis on 1047 patients treated for cGVHD. Among the drugs that can be used against COVID-19, in that study on cGVHD the cheapest resulted chloroquine (9181 US\$), followed by Imatinib (43,965 US\$), and Ruxolitinib (97,807 US\$) [111]. In our opinion, the final list of the “hematological” drugs that could represent promising options in the COVID-19 war might include also Ruxolitinib, Bosutinib, Imatinib and Begelomab. Ruxolitinib probably is the fastest and more powerful agent in the switching off the cytokine storm, as already shown in aGVHD and also in the first COVID-19 cases treated with this JAK1/2 inhibitor. Nevertheless, its doubtful safety from the infective point of view probably might impose at least the need of a careful observation of the immunocompetence in COVID-19 patients, also considering that super-infections have been documented in 8.5 % of them. TKIs could be tried as further options: in different models of inflammations, Bosutinib showed optimal anti-inflammatory properties, already demonstrated by its ability of reverting the pro-inflammatory effects of Dasatinib. In addition, data coming from the experience in CML sustain its good safety profile and sustain the hypothesis of a rapid efficacy also. Imatinib displays a good anti-inflammatory effect, its use is characterized by a low infection rate; it is worth to remember also that Imatinib remain the cheapest drug and probably the TKI most frequently available worldwide. Begelomab, probably for a short period of time, might also be an interesting option for its capacity of destroying the strict negative link between Coronavirus and inflammation actors.

Thus, all considered, in a hypothetical “hematological-driven” algorithm (see graphical abstract), we could imagine using Begelomab for blocking the first steps of infection, Ruxolitinib to rapidly switch off the cytokine storm in the severe/hyperacute phase, and, then to sustain

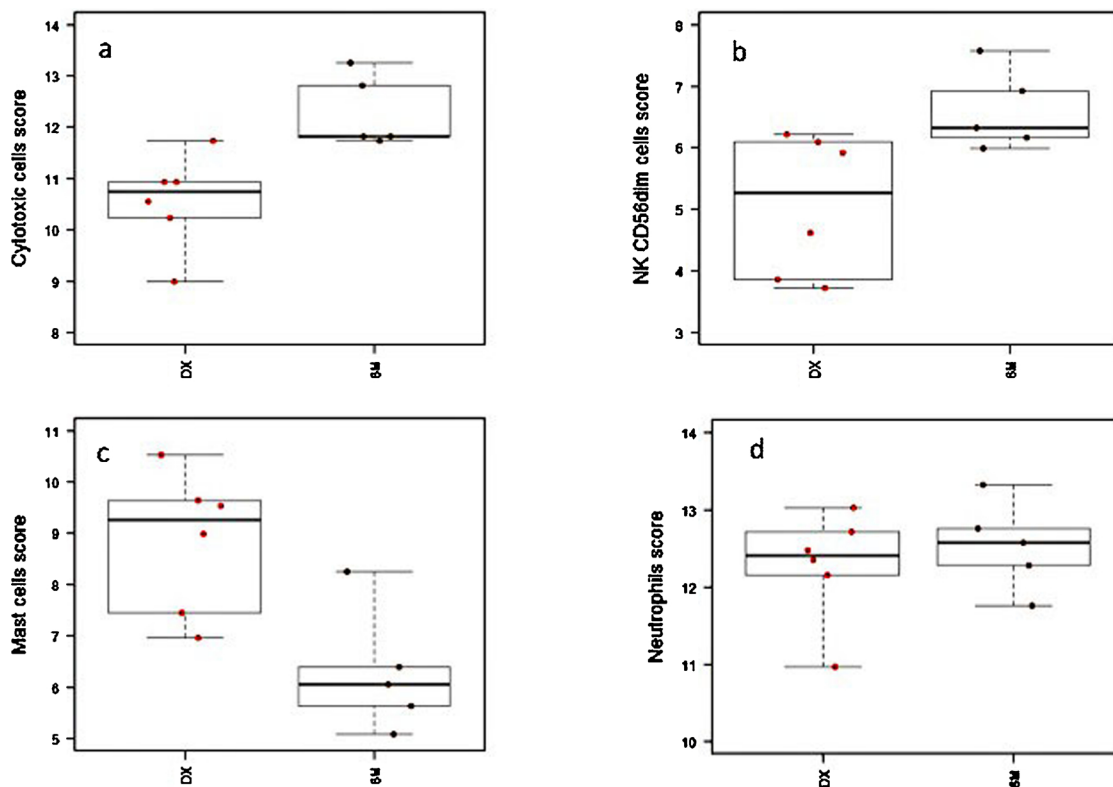


Fig. 2. CML: Box plots representing some cellular types de-regulated by 6 months of treatment with Imatinib.

Changes of mRNAs identifying different cellular populations after Imatinib treatment are here reported. In a) cytotoxic cells (defined as GZMA+, NKG7+, CD94+), whose mRNAs resulted increased by Imatinib; in b) NK cells (CD56 bright), that increased after Imatinib treatment; in c) mast cells (defined as CPA3+, tryptase+, MSGA2+, CCL22+), whose RNAs were decreased by Imatinib; in d) RNAs characterizing neutrophils (defined as FPR1+, SIGLEC5+, CSF3R+, FCAR+), that remained unchanged in respect of diagnosis.

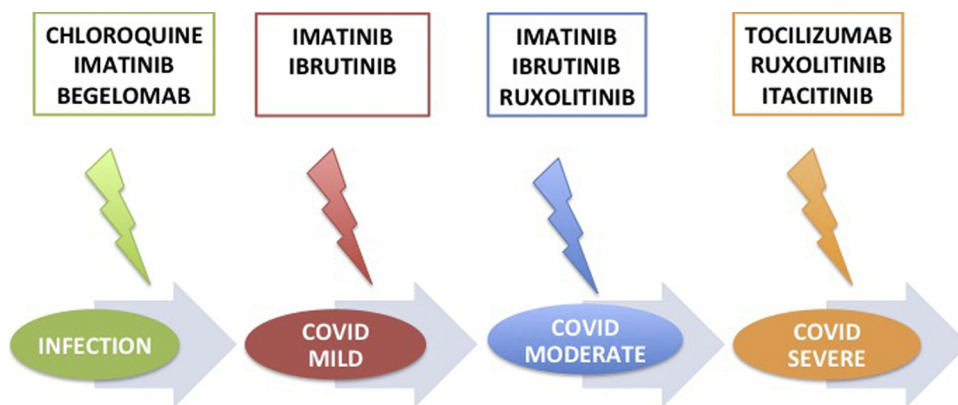


Fig. 3. A possible therapeutic algorithm for COVID-19.

A possible “hematological-based” integrated algorithm for COVID-19 treatment, based on different disease phases, is here represented. In the early stage of SARS-CoV2 infection, chloroquine, imatinib or begeleomab might be useful for blocking the attack of the viral S protein to the CD26 virus receptors, for modifying the lysosome pH or for restoring the anti-microbial autophagy. During an eventual mild COVID-19 phase, the anti-viral host reaction might be sustained by imatinib or ibrutinib, that at the same time might exert also an useful anti-inflammatory action, even if moderate. In the more severe phases of COVID-19, the anti-JAK1/2 inhibitors might be useful, alone or in combination with anti-cytokine monoclonal antibodies, such as Tocilizumab.

Table 3

Table reports the comparison of several features (hematological indication, safety, cost) in different hematological drugs that might have a role in the COVID-19. Abbreviations: MPN = chronic myeloproliferative neoplasms; MAS = macrophage activation syndrome; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; GIST = stromal gastro-intestinal tumor; GVHD = graft-versus-host disease; LNH = non Hodgkin's lymphoma; MM = multiple myeloma.

	Ruxolitinib	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ibrutinib	Begleomab	IFN
Drug formulation	os	os	os	os	os	os	IV	os
Clinical use in GVHD	XX	X	X	X	–	XX	XX	–
Use in hematological diseases	MPNs MAS	CML ALL GIST	CML ALL	CML ALL	CML	CLL MCL	GVHD	CML MPN LNH MM
Infection rate	20 %	5%	11 %	17 %	4%	71 %	10 %	na
Estimated costs	++	+	+	+	+	+++	+++	+

immunity (that Ruxolitinib is not able to do) and the required long-term anti-inflammatory effect by TKIs. On the other hand, the combination of Ruxolitinib with Nilotinib has already been adopted in a phase-I study in CML patients with unsatisfactory molecular response, without significant infections occurrence [112]. In the last few weeks many trials with some of the above mentioned drugs started and will give us soon fundamental information; indeed, the war against SARS-CoV-2 has to be continued: rethinking drugs use with a multidisciplinary approach could be a possible improvement for the final victory.

Author contribution

S. Galimberti and C. Baldini wrote the manuscript; all authors revised and approved it.

Declaration of Competing Interest

S. Galimberti, C. Baratè and M. Petrini were speakers in the events supported by Novartis, Pfizer, Celgene/BMS, Janssen, Roche, Incyte and members of advisory boards for Novartis and Janssen; A. Di Paolo was a speaker for Medac GmbH, Novartis, Roche, Incyte, and was an advisory board member for Novartis; C. Baldini and F. Ferro do not have any conflict of interest.

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