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Rewriting the rules for care of MDS and AML patients in the time of COVID-19

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ABSTRACT

The care of patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) has been radically altered by COVID-19, especially in New York City, the epicenter of the pandemic. Here we summarize how telemedicine, virtual visits, delayed transfusions, and chemotherapy, preferably selecting self-administered medications and visits by home healthcare workers, are employed to minimize exposure of our high-risk population of patients to the virus. The unique challenges of transplants during the pandemic and the consequences of an abrupt halt in all non-essential research activities are described. Not all the changes forced by COVID-19 are detrimental.

A tiny piece of RNA has altered the practice of medicine overnight. COVID-19 impacts every aspect of care for patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) in the City of New York from where we are writing, our hospital is serving as the epicenter of the pandemic within the city. Not all the changes are unwelcome. For one thing, the importance of the patient over paperwork is re-established. For another, caregivers are visiting a majority of patients in the comfort of their homes, a move appreciated by patients while the pandemic rages on and fears of infection are high. Health care professionals for their part have successfully adapted to virtual visits and new ways of remote billing, following often repetitive and frustrating re-training classes. Thanks to electronic health records, care of patients continues uninterrupted as providers work from home. As select benefits of the new approaches dawn upon the participants, it is unlikely we will return precisely to the pre-COVID-19 days. Nor should we. There is no inherent righteousness in the way things were done. This communication summarizes the immediate changes in how we care for our MDS and AML patients during the pandemic.

Weighing the risks of bringing patients to a hospital filled with COVID-19 patients is forcing an examination of what can be achieved remotely. Sending home healthcare workers to check vital signs and obtain blood tests to determine what, if any, treatments or supportive care measures are needed is one important step. Switching therapies that can be self-administered is another. For example, lower-risk MDS patients with deletion 5q presently maintained on erythropoietin support may be better off either taking the injections at home or switching to oral lenalidomide. [1] Anemic patients with ring sideroblasts eligible for therapy with luspatercept would have the same choice. [2] These decisions are reached after careful discussions between patients and caregivers, some electing to continue supportive care measures rather than start on new therapies with limited early information on potential side effects.

Anemia is a predominant issue for the majority of patients with MDS. The decision to transfuse is dependent on patients' symptoms rather than a number on a test report given the predicted shortage of blood products in the coming weeks. Many patients are pushing the limits of their tolerability and delaying transfusions because of the risk involved in coming to the medical center. MDS patients receiving hypomethylating agents are also opting to prolong intervals between cycles, especially if they are beyond six months of treatment, at least for the short term. Protocol guidelines are enforced as strictly as possible for patients on experimental trials, but accrual of new subjects is restricted to therapies offering the potential to be curative or to prolong survival significantly.

In the longer term post-COVID-19 world, many of these changes could be routine as benefits of telemedicine and home healthcare become more apparent and safer with practice. The physical, financial, and emotional benefits of these radical changes for the patient and their caregivers are incalculable.

Given its acuity, treating AML during the COVID-19 pandemic poses

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unique challenges. The American Society of Hematology has offered guidance in managing this difficult group of patients. [3] Since many AML patients require emergent therapy at the time of initial diagnosis, we continue to offer intensive induction chemotherapy with curative intent. Nevertheless, we routinely perform COVID-19 testing prior to the start of induction. In asymptomatic patients testing positive, induction therapy is delayed for up to 14 days if feasible. In most cases, we also recommend postponing induction in symptomatic COVID-19 patients until the course of their infection becomes apparent and patients exhibit some signs of improvement. Lower-intensity therapies such as a hypomethylating agent with venetoclax may be safely given in the outpatient setting [4], thereby reducing patient exposure to novel coronavirus during an inpatient stay, decreasing the frequency of transfusion support, and permitting use of inpatient beds for severely ill patients with COVID-19. Similarly, induction with liposomal daunorubicin and cytarabine can be administered as an outpatient in patients with AML following MDS, therapy-related AML, or those with MDS-related cytogenetic abnormalities. [5] Prophylactic antibacterial, antifungal and antiviral therapy is recommended during induction and through extended periods of neutropenia.

Consolidation with high-dose cytarabine should be offered to patients in remission, provided they test negative for COVID-19 or symptoms have resolved and it is likely the virus is no longer present. Based on findings from the MRC 15 trial, lowering the dose of cytarabine from 3 gm/m^2 to 1.5 gm/m^2 could minimize the duration of myelosuppression without sacrificing long-term outcomes. [6] Moreover, reducing the number of cycles from four to three may also lower the risk of infection. [7] Use of myeloid growth factors further reduces the duration of neutropenia, the risk of infection, and the need for hospitalization.

Although clinical trials are preferred for patients with relapsed or refractory AML, accrual to many studies has been halted due to reduced resources and redeployment of research staff for urgent clinical duties. While intensive salvage regimens may still be considered for these patients, we favor outpatient treatment with an oral targeted agent if a mutation in FMS-like tyrosine kinase 3 (*FLT3*), isocitrate dehydrogenase 1 (*IDH1*), or *IDH2* is detected or a venetoclax-containing regimen.

Patients with low-risk acute promyelocytic leukemia (APL) receive induction with all-*trans* retinoic acid (ATRA) and arsenic trioxide, as this regimen is associated with reduced duration of myelosuppression and risk of infection compared to ATRA-chemotherapy approaches. [8] High-risk patients must still receive a regimen that includes a cytotoxic agent such as an anthracycline or gemtuzumab ozogamcin. QT prolongation is associated with several AML therapies, including arsenic trioxide, gilteritinib, ivosidenib, and enasidenib, particularly if given concomitantly with hydroxychloroquine, chloroquine, and azithromycin, which are commonly used for COVID-19, and other CYP3A4 inhibitors. Therefore, serial ECG monitoring is essential to ensure patient safety.

The COVID-19 pandemic has not spared stem cell transplant, jeopardizing our patients' chance to receive potentially curative therapy. The stakes are already high for stem cell transplant patients, who endure toxic chemotherapy and a weakened immune system suppressed for months. The vulnerability to infections and other complications such as graft-versus-host disease can be successfully managed in a well-resourced healthcare system that we have taken for granted. As COVID-19 pushes hospitals to their limits and beyond, we are now forced to consider the possibility that our patients may not have a ventilator or an ICU bed available to them should they need one. Patients undergoing allogeneic transplantation usually spend up to five weeks in the hospital, and now they spend that time alone as hospitals have moved to no-visitor policies to prevent the spread of COVID-19 to hospitalized patients.

Travel restrictions also impacted stem cell transplants. Often called "the gift of life," bone marrow stem cells donors hail from all countries and ethnicities. Unencumbered by political and geographical boundaries, a patient can receive stem cells from many countries across the globe. In these times of uncertainty, we fear that a patient being prepped for transplant is unable to receive their stem cells. The American Society of Transplantation and Cellular Therapy set forth guidelines about COVID-19. [9] We currently do not know whether this virus can be transmitted in the blood. Given the weakened immune systems our patients have and the toxic treatments they need, we must protect them at all costs. Testing donors for COVID-19, cryopreserving their cells ahead of time, ensuring both patients and donors avoid COVID-19 exposure, and testing patients before the start of conditioning are recommended. Finding a match for stem cell transplant is hard enough; having to exclude a good match or delay transplant further complicates our ability to deliver care.

If translational research is the bridge between basic science and clinical practice, biobanks are its foundation. Our Tissue Repository has been collecting specimens, including blood and bone marrows from patients for the last 35 + years, representing one of the largest biobanks in the world with well-annotated tissue samples. The post-COVID-19 shift to telemedicine means no patients in clinics and no access to fresh samples. Consequences for the lab include loss of valuable ongoing cultures for lack of fresh cells and nutrients, expiration of precious reagents, and wasted experiments. With the implementation of social distancing by federal and state governments, the University suspended non-essential lab research. Therefore, freezing, thawing, and expanding cells after this pause in research will require a significant investment of time and resources. This unexpected break in bench research allows more time for updating pathology and clinical information in the databank, analyzing data, finalizing manuscripts, reviewing experiments, completing lab-books, and yes, writing all those overdue recommendation letters. Lab meetings and discussions regarding grants and future prioritization of projects are taking place through teleconferencing, with designated emergency personnel making the trip physically once a week to ensure that no chemicals are leaking, freezers housing the priceless tissue samples are working, and equipment is safe.

In summary, COVID-19 has fundamentally transformed how we care for our MDS and AML patients, social isolation forcing the practice of remotely delivered healthcare whenever possible. If the best cure for this deadly virus is to avoid it altogether, the same principle should be applied to cancer with greater vigor where a larger scientific and intellectual investment is needed towards early detection and prevention. The pandemic, with all its terrifying consequences, is also a graphic reminder of something beautiful; the oceanic, global connection of humanity. Solutions we seek for cancer patients must be universally applicable, because "Any man's death diminishes me / For I am involved in mankind / And therefore, never send to know for whom the bell tolls / It tolls for thee" (John Donne, Meditation 17, Devotions upon Emergent Occasions).

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