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in the epidemiology and clinical association of sickle cell disease with malaria, and bacterial and viral infections (including SARS-CoV-2), suggests that sickle cell disease should be included in the Integrated Management of Childhood Illness programme to improve outcomes. Provision for sickle cell disease diagnosis and treatment should be incorporated into national health systems programming, with an emphasis on delivering sickle cell disease services in the primary care setting. COVID-19 is expected to herald a global economic recession that might result in a contraction of international funding for health systems development in Africa.

The COVID-19 pandemic is currently overwhelming health systems in high-income countries and so could have an increased effect in low-resource settings in Africa where health services are already overstretched. The effect of COVID-19 on the global economy could cause recession both in Africa and around the world, posing a substantial threat to the delivery of health care in Africa. Every effort should be made to invest in primary health care, and integrate and align sickle cell disease diagnosis and treatment into existing health systems, rather than building new vertical programmes focusing only on sickle cell disease with interventions delivered separately from other health services. African governments should leverage further funding resources to accomplish this aim. The preparation and mitigation stages of the pandemic also represent important opportunities to focus international efforts at rapidly scaling up sickle cell disease-related health-care infrastructure.

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## Effect of the COVID-19 pandemic on cancer treatment and research

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The coronavirus disease 2019 (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly escalated into a global pandemic. Patients with haematological and other cancers,<sup>1,2</sup> and recipients of haematopoietic stem cell transplantation (HSCT), could be at particular risk from COVID-19, since they tend to be

older, have multiple comorbidities, and are often immunosuppressed by their disease or therapy. A retrospective analysis of 355 patients who died of COVID-19 in Italy showed that 20% had active cancer,<sup>3</sup> and a study from 2013–17 of 678 patients who had an HSCT found that 112 (17%) developed human coronavirus infection, of whom 34 had lower respiratory

tract infection.<sup>4</sup> However, evidence regarding the effect of COVID-19 on patients with cancer is inadequate.

The influx of a large number of patients with COVID-19 requiring intensive monitoring and mechanical ventilation has resulted in overloading of hospital systems in the affected regions and countries, disrupting routine treatment of haematology and cancer patients who constitute an especially fragile and vulnerable population, and whose outcomes are likely to be negatively affected if the usual standard of care is delayed. Travel restrictions, patient concerns, regulatory guidance, and sequestering of oncology staff have resulted in many cancer outpatient visits being replaced by telephone consultation, and deferral of some routine therapy, tests, and procedures.

Estimating the risk versus benefit of administering potentially immunosuppressive treatment to patients with cancer with a scarcity of knowledge about this novel disease, and balancing individual versus societal benefits in the new reality of stretched resources, poses acute ethical dilemmas to oncologists. Investigators, government agencies, and professional societies have provided initial experiences and guidance on managing the continued care of patients with cancer during the current period of crisis.<sup>5</sup> Routine visits should be done via telephone or rescheduled, oral medications should be delivered to the patient's home to cover the peak period of the pandemic, and biological samples should be collected and processed at a local facility near the patient's residence. Cancer multidisciplinary team meetings should be done via a virtual platform, and changes should be made to individual treatment plans as needed for the duration of the pandemic.

Patients with leukaemia, lymphoma, or myeloma; those receiving radical radiotherapy for lung cancer, cytotoxic chemotherapy, immunotherapy, antibodies, protein kinase inhibitors, or poly ADP ribose polymerase (PARP) inhibitors; and those with recent bone marrow or stem cell transplants could be especially vulnerable to COVID-19.<sup>5</sup> The European Society of Medical Oncology and National Health Service England have suggested a tiered approach for categorising patients into different priorities for receiving active cancer therapy during the pandemic.<sup>5</sup> Higher priority should be given if the patient's condition is immediately life threatening or clinically unstable, or the intervention is expected to result in substantial overall survival gain or improvement

of quality of life. Oncologists should consider changing intravenous treatments to subcutaneous or oral routes, using longer intervals between immunotherapy regimens, deferring non-urgent supportive therapies, using granulocyte-colony stimulating factor as primary prophylaxis, and discussing treatment breaks for patients on long-term therapy.<sup>5</sup> Radiation treatment should be prioritised for patients with rapidly proliferating tumours and those whose planned radiotherapy has already begun, and hypofractionation should be considered to shorten the treatment duration. Patients with cancer who develop COVID-19 should be treated in the respiratory or intensive care units rather than in the oncology or radiotherapy units.<sup>2</sup>

The COVID-19 pandemic has had a serious and disruptive effect on the conduct of haematology and oncology clinical trials, with both immediate and delayed consequences. In the short term, research staff and resources have been reassigned to manage the rush of patients with COVID-19 at many academic institutions and participating hospitals, and routine clinical research activities have been suspended. Trials testing treatments for COVID-19 have been prioritised. Research-related appointments to hospitals for site selection or qualification, source data verification, drug accountability, audit, and site staff training by contract research organisations (CROs) and sponsors have been cancelled because of travel restrictions. A sharp reduction in recruitment to ongoing trials and a delay in the planned launch of new haematology and oncology studies might be expected during the peak of the pandemic. A delay can also be anticipated in data entry into clinical trial databases owing to study coordinators working remotely with reduced access to the source data. As hospital radiology departments and laboratories are stretched during the pandemic, and to reduce the risk of SARS-CoV-2 infection to trial subjects, some protocol-mandated visits and study procedures, such as tumour assessments and biopsies, have been delayed or cancelled. A delay in imaging will impact progression-free endpoints of ongoing studies, while quality of life endpoints will be affected if patients miss study visits. Most regulatory authorities require that COVID-19 infection and related (serious) adverse events, such as dyspnoea and acute respiratory distress syndrome, be specifically captured and reported.<sup>6</sup> Site staff and monitors will need to be trained in this regard.



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In the medium to longer term, recruitment delays resulting from the pandemic will negatively affect drug development timelines, with damaging financial implications and potential delays in getting promising drugs to patients. An increase in protocol deviations over the duration of the pandemic can be expected, potentially affecting patient safety because of missing or late reporting of adverse events. COVID-19-related deaths could potentially affect survival endpoints in some studies. Cytokine release syndrome is a known toxicity of chimeric antigen receptor T-cell therapy and also occurs in a subgroup of patients with COVID-19,<sup>7</sup> but the effect on ongoing immunotherapy trials is presently unknown.

Regulatory agencies such as the US Food and Drug Administration, European Medicines Agency, and the UK Medicines and Healthcare products Regulatory Agency have issued guidelines on managing clinical trials during the COVID-19 pandemic, stressing the importance of pragmatism and flexibility in tumour assessments and visits (via protocol amendments as necessary), protecting patient safety, clearly documenting protocol deviations, and disallowing prospective protocol waivers.<sup>8-10</sup>

Ensuring patient safety during the pandemic is of utmost priority. Training courses on COVID-19 symptoms, management, and use of personal protective equipment should be implemented. A phone contact with the trial participant should be made the day before the planned visit, to enquire if they have any COVID-19 symptoms. Hospital access should be restricted for vendors, visitors, trial monitors, and auditors. Virtual support services should be implemented for trial participants, and where feasible, remote access to relevant medical charts should be granted to trial monitors to review, verify, and raise queries. Such systems should have robust security and audit trails. Several CROs are responding to this new reality by adapting their usual processes and developing new methods of remote, secure trial monitoring, site staff training, drug accountability, and source data verification and review, while recognising and respecting the disparities in national legislation in different countries with regard to remote access to medical records by CROs and direct shipment of medication to patients.

A discussion between investigators and sponsors should take place to consider withdrawal of optional

trial procedures (eg, biopsies), and to allow laboratory and radiological assessments to be done at an accredited facility closest to the patient. For some investigational products, such as oral medications typically distributed for self-administration, alternative safe delivery methods should be implemented to avoid hospital visits by patients. The implementation of such alternative processes should be as consistent with the protocol as possible, and sponsors and clinical investigators should document the reasons for any contingency measures adopted. Sponsors and clinical investigators should clearly document how restrictions related to COVID-19 led to the changes in study conduct, the duration of those changes, and which trial participants were affected and how. Since radiology services are likely to be stretched during the pandemic, central imaging review should be instituted to ensure good quality of data for clinical trial patients.

COVID-19 has had a huge and negative effect on cancer treatment and research. We hope that with the support of all stakeholders, patients with cancer and trial participants can receive the best possible care even in these exceptionally difficult times.

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## Management of patients with multiple myeloma during the COVID-19 pandemic



A novel coronavirus of zoonotic origin emerged in China at the end of December 2019. The infection, named coronavirus disease 2019 (COVID-19), is now spreading worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA beta-coronavirus, which has a phylogenetic similarity to another known coronavirus, SARS-CoV-1, the causative agent of SARS responsible for a major epidemic in 2003. The contagious potential of this virus is proving to be very rapid and unpredictable. As of April 20, 2020, more than 2.4 million cases of COVID-19 have been confirmed resulting in more than 150 000 deaths worldwide. Mortality can be as high as 15% in older patients and those with comorbidities.<sup>1</sup> The severity of COVID-19 is classified into four types: mild, ordinary, severe, and critical. In addition, approximately 18% of patients are estimated to have asymptomatic SARS-CoV-2 infection.<sup>2</sup> At present, no treatment options have been approved in Europe, and no vaccine is available. Avoiding exposure by adhering to recommended hygiene procedures, isolation of infected people, and social distancing are the only prevention strategies recommended by the WHO.

Risk factors for COVID-19 severity and death include increased age and the presence of comorbidities such as diabetes, hypertension, or cardiac diseases.<sup>1</sup> In addition, data from China suggest that patients with cancer have a significantly higher incidence of severe events (including intensive care unit admission, need of assisted ventilation, and death) after contracting SARS-CoV-2 than patients without cancer (seven [39%] of 18 patients with cancer vs 124 [8%] of 1572 patients without cancer;  $p=0.0003$ ).<sup>3</sup> Another study<sup>4</sup> reported that patients with cancer were

twice as likely to be infected with SARS-CoV-2 than patients without cancer. Importantly, this study suggests that hospital admission and recurrent hospital visits, inherent to the management of patients with cancer, are potential risk factors for SARS-CoV-2 infection. Data regarding patients with haematological malignancies are scarce. Nevertheless, we can expect that the SARS-CoV-2 infection pattern will be similar to that of patients with solid cancers. Recommendations for the management of patients with solid cancer and haematological malignancies have been published (eg, from the French High Council for Public Health). However, these guidelines are general and more specific ones could be required for individual types of malignancies, including multiple myeloma, as patients with this disease have severe humoral and cellular immune deficiency.<sup>5</sup> This deficiency is associated with impaired responses to tumour, microbial, and vaccine antigens. Therefore, attention should be paid to this high-risk population during the ongoing COVID-19 outbreak. Here, we summarise some recommendations to help with the management of patients with multiple myeloma during the COVID-19 pandemic (table).

High-dose melphalan and autologous haematopoietic cell transplantation (AHCT) remain the standard of care for fit patients with newly diagnosed multiple myeloma. Although haematopoietic recovery after AHCT occurs within 3 weeks, full recovery of T-cell and B-cell function can take months to years, and vaccine responses during this period are typically poor. Furthermore, the COVID-19 outbreak is expected to be associated with a shortage of ventilators and intensive care beds, putting patients receiving treatment for multiple myeloma at increased

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