Prevalence of CMBs was also associated with lower platelet counts at the time of SWI and with higher organ bleeding scores, but not with mucosal and skin bleeding scores or with the number of previous treatments, age, and sex. In summarizing their findings, Cooper et al suggest that applying a treatment threshold based on platelet count alone could result in some patients being overtreated and others undertreated, and that SWI could provide a specific noninvasive biomarker of central nervous system hemorrhagic tendency, enabling further stratification of disease phenotypes. The inability to link the occurrence of a CMB to a specific time during the course of the disease is a major limitation of this study. Also, as suggested by the authors, longitudinal prospective studies are needed, in particular, to prove that there are increasing numbers of CMBs over time. In a similar study limited to children and adolescents, only 1 case with a single CMB was found among 27 prospectively investigated subjects, all with a platelet count $\leq 10 \times 10^9$/L at diagnosis or upon symptomatic relapse.[7] Reassuringly, in patients with severe hemophilia, a much more harmful hemorrhagic disease, CMBs were only slightly increased compared with healthy controls.[8]

Appropriately, Cooper et al do not recommend brain SWI outside of a research setting. Minor cognitive symptoms with memory and concentration difficulties have been reported in some patients with ITP, but they were ascribed to emotional distress and often associated with other common subjective symptoms like fatigue[9] Cautiously, the authors avoid making conjectures on the possible ominous long-term neurological consequences of CMBs in ITP.

This excellent study raises more issues than it resolves. It will encourage new areas of investigation to clarify the significance of CMBs in ITP and to better understand the mechanisms underlying different bleeding phenotypes beyond the simplistic parameter of the platelet count.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood.2020008425

CLINICAL TRIALS AND OBSERVATIONS

Comment on Vijenthira et al, page 2881

Under COVID of the night

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In this issue of *Blood*, Vijenthira and colleagues report that patients who have 2 life-threatening conditions, a hematologic malignancy and infection with the virulent microbe COVID-19, face a risk of dying that is ~1 in 3.[1]

Severe acute respiratory syndrome coronavirus 2 proved to be the perfect pathogen for a world unprepared. Because it is a novel virus, few people had any immunity, although some may have been spared its nastier consequences from past coronavirus infections. It spread efficiently, with a reproductive number (R0, indicating the contagiousness of the disease) between 2 and 3, meaning 1 infected person transmitted the virus to 2 or 3 others. Compare that to the R0 for the influenza pandemic of 1918, which was 2.0, or of 2009, which was 1.7.[2] It proved deadly in higher numbers of people than did influenza, with a case fatality rate of ~3% in the general populations of the United States. Our global economy and general wanderlust enabled infected hosts to spread the virus to those in immediate filial and social circles, and nearby or far-away states and countries efficiently, whereas geopolitics helped delay recognition of the seriousness of the pandemic and thwart implementation of measures to clamp it down.

Particularly vulnerable populations to COVID-19 proved to be the aged and infirm, who are more likely to have complicated comorbidities and might have an exaggerated inflammatory immune response to the virus[3]; those already at risk for adverse health outcomes based simply, and tragically, on their race[4]; and people with immune systems that were functionally compromised. Patients with hematologic malignancies are potentially ideal viral breeding grounds, with immune systems already corrupted and rendered at least somewhat incompetent by cancer, and by both cytotoxic and immunologic therapies which, by design, further suppress immune function. A recent study of >3000 patients hospitalized with COVID-19, of whom 100 had cancer, showed that patients with hematologic malignancies had higher COVID-19 viral loads, and that this was, in fact, associated with higher mortality rates.[5]

Vijenthria et al conducted a systematic review of studies published in PubMed and EMBASE databases, and reported on patients with hematologic malignancies and COVID-19 to determine risk of death and serious complications, such as intensive care unit admission and ventilation support. A total of 34 adult and 5 pediatric studies were included, comprising 3377 patients, the majority of which were descriptive cohort studies. Types of hematologic malignancies included lymphoid malignancies (~66% of included patients), plasma cell dyscrasias (12%), myeloproliferative neoplasms (8%), acute leukemias (8%), and bone marrow failure syndromes (7%).

The pooled risk of death was 34%, higher (39%) for the 2361 inpatients, and lower (4%) for the 102 pediatric patients. Patients had about a 21% chance of requiring intensive care and 17% chance of being placed on mechanical ventilation. As expected, younger patients (<60 years) had a mortality risk almost half that of older patients (≥60 years, 25% vs 47%, $P < .00001$), and disparate health outcomes based on race were reinforced, with non-White patients more than twice as likely to die compared with White patients (relative rate = 2.2, $P = .003$). Recent receipt of anticancer therapy did not affect mortality risks, but cancer subtype may have, with risk of death highest for those with acquired bone marrow failure syndromes and acute leukemias. The study may have overestimated COVID-19–related deaths, as it was enriched by hospitalized patients, and as patients with advanced stage cancers may have died anyway from their competing risk.

I came of professional age in an era when practicing evidence-based medicine was held up as the gold standard for competent and trusted physicians. When faced with a new and poorly defined contagion, with conflicting data about its etiology, transmissibility, lethality, and prevention, and few rigorous studies providing insight into this basic information, I feel unmoored.

This systematic review provides us with data we can use in the common conversations we are now holding daily with our hematologic malignancy patients: That yes, they should continue to practice social distancing, wear masks, engage in good hand hygiene, and avoid risky infectious behaviors; that if they catch the virus, their chance of landing in an intensive care unit is 1 in 5, and of requiring mechanical ventilation is 1 in 6. In fact, their chance of dying from COVID-19 is >10 times higher than the general population. However, as we weigh the relative risks and benefits of initiating treatment of their cancers, we can rest easier that chemotherapy does not appear to increase their chances of dying from the virus. We await population-based studies to answer the question of whether our patients are also at higher risk of catching COVID-19.

The song *Undercover of the Night* by the Rolling Stones[6] explores political corruption in Central and South America in the 1980s, an area of the world also hit hard by COVID-19. Similar to the virus' path, the sinister forces of which Mick Jagger sings take people's lives by dark of night, while the rest of us "curl up tight," hoping that we also will not get stricken. As we await widespread implementation of an effective vaccine, our best medicine against COVID-19 is to exhort our patients to engage in preventive practices to avoid a substantial risk of dying, so that we can all walk the streets safely again one day.

Conflict-of-interest disclosure: The author serves on advisory boards for Celgene/BMS, Takeda/Millenium, and Pfizer. ■

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DOI 10.1182/blood.2020009377

HEMATOPOIESIS AND STEM CELLS

Comment on Fidanza et al, page 2893

A NEWral approach for HSC production in vitro?

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In this issue of *Blood*, Fidanza et al elegantly describe the single-cell transcriptome of hematopoietic stem and progenitor cells (HSPCs) derived from human pluripotent stem cells (hPSCs) and compared it with human fetal liver progenitors using an artificial neural network.[1]

The ultimate challenge in the field of developmental hematopoiesis is understanding the complex differentiation landscape of HSPCs in order to reproduce in vitro, and eventually in vivo, the proper environmental cues to support long-term, multilineage hematopoietic stem cells (HSCs). Blood progenitors appear in the embryo in distinct hematopoietic waves, which differ from each other by their lineage output.[2] Identification of specific cellular markers to isolate these progenitors is essential to explore the hierarchical relationships during developmental hematopoiesis. For this reason, integrative bioinformatics approaches are being used to improve our understanding of the cellular and molecular factors associated with the emergence of HSCs in vivo and in vitro.[3]

Fidanza et al reported an elegant, well-conducted study in which human induced pluripotent stem cells–derived HSPCs were sequenced and compared at the single-cell level with in vivo counterparts. More than 40 000 cells were sequenced in the experiments. In the first experiment, the authors selected the $CD235a^{-}CD43^{+}$ suspension cell population in order to exclude progenitors originating from the primitive wave. This heterogeneous mix of progenitors nicely clustered into clearly separable populations of uncommitted, immature progenitors and cells committed to megakaryocyte, erythroid, and granulocyte lineage, with the identity of each population marked by a unique repertoire of expressed genes. With a combination of semisolid clonogenic assays and a chimeric coculture system, the authors functionally