Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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clear and that the combination could also be useful in selected potential candidates for allogeneic HSCT.

The study by DiNardo and colleagues consolidates the combination of venetoclax with a hypomethylating agent, in this case 10-day decitabine, as a potential standard of care in patients with AML and not candidates for intensive chemotherapy. The study also shows the feasibility of associating particular targeted drugs to this combination in patients with a druggable molecular profile. In this regard, the results of the association with FLT3 inhibitors are striking in terms of activity, both in newly diagnosed (CR and CRi in 9 of 10 patients) and in previously treated patients (5 of 12), many of whom had already previously received hypomethylating agents or FLT3 inhibitors.

Venetoclax in combination with 10-day decitabine with a median of 3 cycles, compared with decitabine monotherapy, shows a higher proportion and deeper responses, improved overall survival, with theoretically less costs and toxicity. However, a direct comparison with the FDA-authorised scheme of 5-day decitabine plus venetoclax is still required. Furthermore, since the combination is highly active in the worst-case scenario, a clinical trial in younger patients with AML across all risk subgroups could be considered.

We declare no competing interests.

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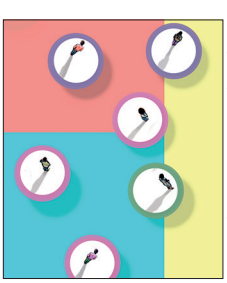
COVID-19 and haematological malignancy: navigating a narrow strait

Patients with haematological malignancies face unique infectious risks. Not only do their cancers typically directly affect the immune system, but therapies can cause severe myelosuppression and lymphodepletion, especially in curative settings. Vigilance to avoid life-threatening infection is a part of life for these patients and is crucial in medical decision making. With this context, the COVID-19 pandemic has understandably shaken this community, and more data to guide management are needed.

In *The Lancet Haematology*, Francesco Passamonti and colleagues report the results of a multicentre, retrospective study aimed at investigating factors associated with mortality in an Italian cohort of 536 patients with haematological malignancies and laboratory-confirmed, symptomatic COVID-19.[1] They found that mortality in this cohort was meaningfully higher when compared with a cohort of patients with haematological malignancies but not COVID-19 (standardised mortality ratio 41·3, 95% CI 38·1–44·9) and with the general Italian population with COVID-19 (2·04, 1·77–2·34).[1] They used multivariable Cox regression to identify factors independently associated with increased mortality, including older age (hazard ratio 1·03, 95% CI 1·01–1·05), progressive disease (2·10, 1·41–3·12), and several specific cancer diagnoses (hazard ratios ranging from 1·30 to 3·49, using).[1] To our knowledge, this is the largest published cohort study dedicated to the outcomes of patients with haematological malignancies and COVID-19, and informs clinical practice.

The finding that patients with haematological malignancies are at increased risk of mortality due to COVID-19 corroborates other studies.[2–5] The magnitude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of the risk has implications for medical decision making. Although appropriate therapy should not be withheld, patients and their physicians can take precautions to reduce risks of COVID-19, such as choosing oral over intravenous regimens where there is equipoise, using growth factor support more judiciously, or reducing surveillance laboratory and radiographical evaluations when possible.[6,7]

In addition to the high baseline risk posed by COVID-19 to patients with haematological malignancies, the infectious complications associated with many cancer therapies loom large. Passamonti and colleagues' finding that recency of therapy had no association with mortality[1] provides reassurance of the general safety of cancer treatment in this era. Although this is consistent with studies of patients with cancer in general, including our analyses of the COVID-19 and Cancer Consoritum cohort,[8] the specific finding that this holds for patients with haematological malignancies is novel and is an important contribution to the literature. It is important to note that this does not guarantee the safety of every specific treatment in every clinical scenario. Receipt of multiple distinct lines of cytotoxic therapy has a known association with increased risk of life-threatening infections other than COVID-19, and this might also hold with COVID-19.[9] The risk–benefit ratio of later-line therapies with questionable benefit, particularly in light of the finding that patients with progressive disease have higher rates of morbid COVID-19, might therefore not be favourable when studied individually. Widely used non-cytotoxic therapies could pose occult risks—eg, anti-CD38 monoclonal antibodies, which can have deleterious effects on natural killer cell populations.[10] Whether it is safe to deploy such agents during the pandemic remains unclear. Investigations of the detailed associations between specific therapies and clinical scenarios with COVID-19 outcomes should be a priority of future work.

Although informative, Passamonti and colleagues' findings must be interpreted cautiously. The precise estimate of mortality reported is probably higher than that of the global population of patients with haematological malignancy and COVID-19. The composition of this cohort, 84% of whom were inpatients, suggests bias in enrolment favouring patients with severe disease; the relatively low rate of intensive care unit admission (18% of patients) might reflect rationing of health-care resources away from the patients in the cohort (and was well documented in northern Italy during the enrolment period); and the high mortality reported in patients with mild disease (48 [18%] of 268 patients) is inconsistent with previous studies. The degree to which mortality is overestimated is likely to be non-random, which could create apparent differences in mortality between groups that might influence the modelling results. The model reported does not adjust for several known risk factors for COVID-19 mortality, such as smoking and functional status; future studies should account for these where possible. The short median follow-up interval of 20 days highlights that the associations identified are with early mortality and might not reflect an entire COVID-19 course; although it remains too early in the pandemic to collect mature long-term outcome data, this should be recognised when applying these data to patient care.

In conclusion, Passamonti and colleagues have advanced our understanding of the unique risks the COVID-19 pandemic poses to patients with haematological malignancies. Although it is appropriate to fear COVID-19, as many health-care systems return to normalcy, deferring treatment is not the optimal response. Patients and their physicians should be mindful of this when deciding on how best to manage living through the COVID-19 pandemic with haematological malignancies.

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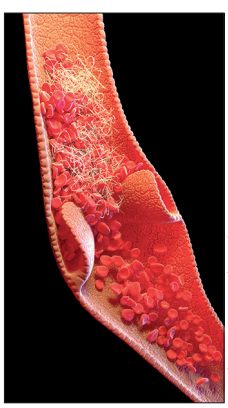
Heparins as cancer therapy: in theory, they should have worked

Cancer-associated venous thromboembolism is a frequent complication of malignancy and is associated with considerable morbidity and mortality. The median overall survival after a first cancer-associated thrombotic event is 6–12 months, and several studies show it is one of the leading causes of death in patients with cancer.[1] Because of the efficacy of low-molecular-weight heparins to reduce the risk of venous thromboembolism in patients with cancer,[2] it is reasonable to hypothesise that venous thromboembolism prevention with this treatment would also improve survival. This clinical hypothesis is supported by a large body of laboratory research showing that heparins can mitigate, if not blunt, several pathways accountable for tumour progression and cancer treatment resistance, including tumour angiogenesis, tumour cell adhesion and migration, metastasis, and immune evasion.[3] Therefore, low-molecular-weight heparins might not only improve disease control and survival in patients with metastatic cancers, but might also reduce recurrence risk and hence improve the potential of cure in the adjuvant setting, irrespective of venous thromboembolism occurrence.

In *The Lancet Haematology*, Holger Schünemann and colleagues[4] report a large individual participant data meta-analysis on low-molecular-weight heparin thromboprophylaxis in patients with ambulatory cancer. To assess the effect of low-molecular-weight heparins on risk of death, venous thromboembolism, and bleeding, the authors combined patient-level data from 14 randomised controlled trials (low-molecular-weight heparins *vs* control), including more than 8000 patients from more than 50 countries. Beyond the technical strengths of this analysis, including an individual participant data framework, the authors are to be commended for doing clinically meaningful subgroup analyses.

By contrast to the theory of the effectiveness of heparins as cancer therapy, the individual participant data meta-analysis by Schünemann and colleagues[4] did not find any evidence for a meaningful survival benefit of prophylactic low-molecular-weight heparins in patients with cancer after 1 year (adjusted relative risk [RR] 0·99, 95% CI 0·93–1·06). Overall mortality during the study was 2690 (65·0%) of 4139 participants in the low-molecular weight heparin group and 2749 (66·4%) of 4139 in the control group.

The authors expanded their analyses to clinically-meaningful subgroups defined by cancer type, cancer stage, and performance status, but did not find any interactions suggesting a survival benefit of low-molecular-weight heparins in any of these groups. This main finding is subject to some limitations. First, the included studies were very heterogenic regarding tumour types, antineoplastic treatment schedules, stage of cancer, and type, dose, and duration of anticoagulation, with some examined anticoagulants not approved for clinical use. Moreover, most of the underlying studies were not designed for defining the effect of thromboprophylaxis on mortality, with mortality often being a secondary or tertiary endpoint. Standard efficacy outcomes of cancer therapy studies, including progression-free survival for metastatic disease and recurrence-free survival for the adjuvant treatment setting, were also not assessed. Additionally, an individual participant data meta-analysis, although the underlying studies are randomised, still represents an observational research study. These limitations should be taken into account when discussing the mortality findings of the study. Nonetheless, the study by Schünemann and colleagues[4] is important and represents the most conclusive evidence to date on the concept of the use of heparins as cancer therapy. Several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