



# Advanced palliative care medicine in hematological oncology

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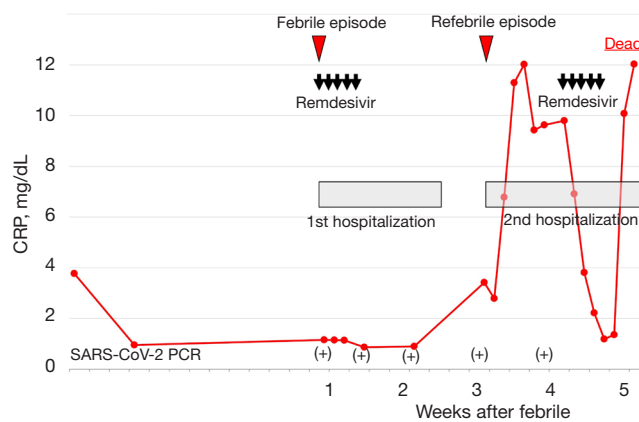
One of the challenges in supportive care for hemato-oncological diseases is the unmet need for care. Hemato-oncological supportive care is arduous because hematological palliative care therapy is performed not only for palliative care patients but also for advanced care patients. This indicates that hematological support encompasses early/advanced conditions, benign/malignant diseases, and young/elderly individuals in a wide array of hemato-oncological patients. A major therapeutic dilemma of palliative medicine in hemato-oncology includes the therapeutic management of cytopenia and infection. Limited literature exists regarding the abovementioned issue, which is not even clearly elucidated in palliative care medicine textbooks. In such scenarios, an updated and summarized review regarding palliative therapy in hemato-oncology is warranted.

Chan *et al.* summarized the current standard of supportive care in hemato-oncology (1). Two major topics include transfusion and infection management. The authors provided a trigger value as an indication for transfusion as follows: hemoglobin <7.0 g/dL for red blood cells and platelets (PLT) below  $(10.0-20.0) \times 10^9/L$  for PLT concentration. This value was established to decrease the frequency of blood transfusion. Because a transfusion-refractory status of PLT exists occasionally, minimally required PLT transfusion is optimal. For the sake of blood transfusion reduction, a clinical blood transfusion policy

“patient blood control” might be beneficial (2), which has been utilized for a few decades. The coronavirus pandemic has accelerated this need. Because the supply chain for providing blood products has been disrupted by the coronavirus disease 2019 (COVID-19) outbreak (3), each physician should stringently evaluate the need for blood transfusion of each patient based on each patient’s disease condition. One of the conservative strategies is to lower the trigger value for blood transfusions. Prophylactic blood transfusion has been investigated in patients who underwent stem cell transplantation in several clinical trials (4-6). In recent randomized control studies, the threshold of PLT transfusion was  $10.0 \times 10^9/L$ . Prophylactic PLT transfusion when PLTs fall  $<10.0 \times 10^9/L$  can prevent bleeding (7). Regarding red blood cells, a hemoglobin value of 7.0 mg/dL has been confirmed as the threshold in many trials (8). In the present consensus, this trigger value is almost conclusive.

Infection management in patients with hematological diseases is crucial, particularly in those with leukopenia, neutropenia, or lymphopenia. In the review article by Chan *et al.*, the authors advocated that infectious diseases in these immunocompromised patients should be managed according to the Infectious Diseases Society of America guidelines (9). This is the gold standard in managing opportunistic infections in immunocompromised patients, such as in hematological diseases, including during chemotherapy. Chan *et al.* reviewed and recommended the

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**Figure 1** The clinical course of the patient with malignant lymphoma and coronavirus disease 2019. CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

prophylactic use of antimicrobials for bacterial, fungal, and viral infections. However, this is a guideline intended for cancer patients with intensive or aggressive cancer therapy. A more intensive treatment of infectious diseases in end-stage cancer patients could be inadequate, depending on the case. Recently, many novel agents against infections have become available, and a majority of these drugs are costly. For instance, new antifungals are continuously developed every 5 years (10). Palliative care physicians should prescribe these antifungals as indicated and on a case-to-case basis, as most end-stage cancer patients suffer from or occasionally die of inevitable infection.

Lastly, we advocate the importance of end-of-life (EOL) care in hemato-oncology patients, particularly in the advent of the worldwide pandemic, because during the COVID-19 era, EOL care is highlighted due to the high risk of morbidity and mortality; therefore, extreme precaution is required for these populations. Patients diagnosed with hematological diseases complicated by COVID-19 often have a poor prognosis, not only because of the COVID-19 infection but also due to their hematological comorbidity (11). The mortality rate was as high as 62% (11) in Japanese patients with hematological diseases. This is from inpatient setting data. We encountered a case of malignant lymphoma complicated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Figure 1). This was a case of an 87-year-old man who was diagnosed with penile lymphoma. He administered rituximab ( $375 \text{ mg/m}^2$ ), pirarubicin ( $25 \text{ mg/m}^2$ ), vincristine

( $0.65 \text{ mg/m}^2$ ), and cyclophosphamide ( $480 \text{ mg/m}^2$ ) (THP-COP) therapy due to his age. The chemotherapy was administered every 3 weeks, which was uneventful, and the second course of chemotherapy was administered at regular intervals. On day 20 of the second course of chemotherapy, he was infected with SARS-CoV-2. He was admitted to the COVID-19 care unit and was given nasal oxygen at 1–2 L/min and received remdesivir (200 mg on day 1 and 100 mg subsequently for 4 days). He responded well to the antiviral therapy and supportive care. After being febrile for 3 days ( $\geq 101^\circ \text{F}$ ), his fever lysed, and oxygen inhalation was discontinued. The patient was discharged after a 12-day observation period, although his SARS-CoV-2 polymerase chain reaction (PCR) test had been positive throughout his inpatient treatment.

Four days after his discharge, fever was again noted, and he tested positive for SARS-CoV-2 via PCR with bilateral pneumonia on chest radiography (Figure 1). In this admission, he was diagnosed with bacterial pneumonia secondary to COVID-19 infection. He was treated with dexamethasone (dexamethasone  $3.3 \text{ mg/day}$  for 7 days), remdesivir (200 mg on day 1 and 100 mg subsequently for 4 days), and piperacillin/tazobactam for the bronchopneumonia. Sputum culture identified a colonized pathogen, *Staphylococcus haemolyticus*. During his hospitalization, he deteriorated, and his pneumonia progressed. Oxygen inhalation at 1.0 L/min was administered. He tested positive for SARS-CoV-2 via PCR during his entire treatment course. Initial therapy against SARS-CoV-2 and bacterial infections improved his fever and respiratory condition. The laboratory tests also improved, probably secondary to the dexamethasone therapy. However, on the 15<sup>th</sup> hospital day, in his second febrile episode, he died of respiratory failure.

Poor prognosis in hematologic malignancy (HM) with COVID-19 was demonstrated in this case, that is, an overt comorbidity in long-standing immunocompetency and poor recovery. The patient in this case also had hypertension and cerebral infarctions. Representative in this case, the poor prognosis of COVID-19 in HM patients is heavily affected by their immunocompetency, which is enhanced by the hematological disease and chemotherapy.

Isolation of a SARS-CoV-2-infected patient is a critical issue (12), especially during the EOL period. Due to the anticipation of transmission of COVID-19 from a severely infected patient, even patients with a do-not-attempt-to-resuscitate status are isolated not only from health care workers but also from their families. Advanced

care planning (ACP) is also a clinical topic that involves a patient's quality of life (QOL). The families of COVID-19 patients in EOL care are likely unable to communicate with the patient. In Japan, families of deceased patients due to COVID-19 are prohibited from seeing them even after discharge from the hospital. A misconception of disease transmission from deceased patients has been falsely communicated to the public. This is indeed an unfortunate situation for the bereaved. We are hopeful that the families of the deceased patients with COVID-19 can bid farewell properly to ensure effective EOL care. The patient's dignity and QOL should be respected according to the tenets of the ACP.

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