NCCN Hematopoietic Growth Factors

Short-Term Recommendations Specific to Issues with COVID-19 (SARS-CoV-2)

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Note: For acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), we defer to the respective disease-specific recommendations.

Background: *We have encountered unique issues related to caring for cancer patients in the current COVID-19 pandemic and have realized that our current standard-of-care NCCN Guidelines do not adequately address some of these issues, such as the limited blood supply, possible impact on those with active infection, and measures that might shorten or prevent hospitalization. These issues may wax and wane, and may require continuous communication with local Blood Bank directors to optimize treatment.*

Neutropenia-Related Considerations

- Expand prophylactic use of granulocyte colony-stimulating factor (G-CSF) to minimize risk of febrile neutropenia, thus not adding to the overwhelming number of cases in emergency rooms (ERs) and hospitals.
    - Change threshold for use of G-CSF with regimens from only high risk (>20% risk of febrile neutropenia) to intermediate (10%–20% risk of febrile neutropenia) or high risk (for reference to usual standard of care, see MGF-1 in the NCCN Guidelines for Hematopoietic Growth Factors).
    - *Cautionary statement: Physicians may wish to avoid use of or discontinue G-CSF in case of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19 to avoid increase in pulmonary inflammation or hypothetical risk of increasing inflammatory cytokines associated with adverse outcome.*
- Expand therapeutic use if patients previously not on G-CSF develop febrile neutropenia to include all patients, not just those with a risk factor for complication. The primary goal would be to minimize days of hospitalization

(for reference to usual standard of care, see MGF-4 in the NCCN Guidelines for Hematopoietic Growth Factors).
    - *Cautionary statement: Physicians may wish to avoid use of or discontinue G-CSF in case of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19 to avoid increase in pulmonary inflammation or hypothetical risk of increasing inflammatory cytokines associated with adverse outcome.*

- Consider use of G-CSF to accelerate post-hematopoietic cell transplant recovery of absolute neutrophil count (ANC), to minimize days of hospitalization (for reference to usual standard of care, see MGF-C in the NCCN Guidelines for Hematopoietic Growth Factors). Some centers also utilize G-CSF post related and unrelated allogeneic transplants, while others do not, as there are concerns including possible increased risk of graft-versus-host disease (GVHD) (Ringden et al).
- To avoid risk of contracting COVID-19 by frequent visits to an outpatient center, consider self-administration of daily filgrastim or use of long-acting pegfilgrastim (1–3 days post chemotherapy) or on-body injector pegfilgrastim use 1 day after chemotherapy.

Anemia and Erythropoietin-Stimulating Agent (ESA)–Related Issues Given Regional Limited Blood Supply

- Considerations for conserving limited blood supply:
    - http://www.aabb.org/advocacy/regulatorygovernment/Documents/Tips-for-Hospitals-Extending-the-Blood-Supply.pdf
    - Consider “restrictive” threshold for RBCs transfusion, e.g., -Hgb <7 g/dL as has been studied in intensive care units (ICU) (Cable et al) and hematopoietic cell transplantation (HCT) patients (Tay et al). Threshold can be increased for patients with cardiopulmonary or other comorbid conditions.

- Considerations are below for broadening use of ESAs with blood supply shortages, as the Risk Evaluation and Mitigation Strategy (REMS) program was discontinued, and there are no recent data that use of ESAs targeting lower Hgb threshold accelerates cancer progression:
    - Currently, the guidelines for use of ESAs do not recommend use for patients with cancer who are not on treatment, those who are receiving minimally myelosuppressive regimens, or those who are being treated with curative intent (for reference to usual standard of care, see ANEM-3 in the NCCN Guidelines for Hematopoietic Growth Factors). Despite these recommendations, not all studies confirm reduced survival with ESA use in patients with cancer. The BRAVE study in metastatic breast cancer (Aapro et al) meta-analysis of darbepoetin in chemotherapy-induced

anemia (Ludwig et al) and meta-analysis of ESAs in cancer (Glaspy et al) demonstrated no adverse impact on survival due to cancer progression.

- Therefore, in light of the potential for blood shortages with the COVID-19 pandemic, we suggest, **in the short term,** broadening the use of ESA therapy +/- IV iron supplementation to manage anemia in patients with malignancy requiring blood transfusion support (for reference to usual standard of care, see ANEM-3 in the NCCN Guidelines for Hematopoietic Growth Factors).
    - Response to ESAs is improved with parenteral iron supplementation (for reference to usual standard of care, see ANEM-B in the NCCN Guidelines for Hematopoietic Growth Factors).
    - Timing of administration of ESAs or iron could coincide with usual blood draws or visits.
- *Cautionary statement*: An increased risk of thrombosis has been observed with ESAs. Therefore, use the lowest dose of ESA sufficient to avoid transfusion. For example, hold ESA for Hgb ≥10.

- Considerations are below for alternatives during severely limited blood supply; broaden use of guidelines for those "who refuse blood transfusions" to include when transfusion support is not available (for reference to usual standard of care, see ANEM-C in the NCCN Guidelines for Hematopoietic Growth Factors).
    - Limited blood draws (reduce frequency, reduce volume)
    - Utility of iron infusions in improving response to ESAs with transferrin saturation <50%, ferritin <800 (concept of "functional" iron deficiency)
    - Assessment of baseline values for B12 and folate and consider nutritional supplements: B12 500–1000 mcg PO daily and folate 1 mg PO daily

Thrombocytopenia-Related Considerations Due to Limited Blood Product Supply

- Lowered threshold for transfusion: Platelet count <10K (some centers using <20K for outpatient), modified for patients with bleeding. Consider adding prophylactic antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid) for patients with platelet counts under 10K for which no platelets are available due to blood supply shortage or alloimmunization without suitable human leukocyte antigen (HLA)-matched units. Hold antifibrinolytics for platelet count >30K and do not use in patients with embolic stroke, thromboembolism, or urinary tract bleeding.
    - Consider thrombopoietin mimetics (eg, romiplostim) for patients with severe thrombocytopenia post cancer chemotherapy (solid tumor; eg, Soff et al), start for platelet count <30–50K and then discontinue for platelet count >75–100K.
    - *Cautionary statement: There is an increased risk of thrombosis.*

- *Note: There is not a current thrombopoietic mimetic section of the V.2.2020 NCCN Guidelines for Hematopoietic Growth Factors.*

References:

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