FEATURE

Literature-based followup recommendations

Part 5: Common hematologic problems in oncology patients

Malcolm Brigden, MD, FRCPC, FACP; Carolyn Owen, MD, MDres(UK), FRCPC; Martina Trinkaus, MD, FRCPC

ABSTRACT

Hematology problems involving anemia, bleeding or thrombosis are exceptionally common in cancer patients. Many smaller Canadian cancer centres are without staff hematologists to manage such common hematology problems and there may not be other hematology expertise available locally. In these instances, general hematology services are often provided by regional cancer programs. This article provides a literature-based approach to the management and followup of cancer-related anemia, thrombocytopenia, coagulopathies and thrombosis. The emphasis is on a practical overview as opposed to the comprehensive details found in standard clinical texts. Key words: cancer-related anemia, thrombocytopenia, bleeding disorders, clotting abnormalities, thrombosis

ANEMIA IN CANCER PATIENTS

Anemia is exceptionally common in cancer patients and is usually multifactorial in nature. In addition to blood loss, bone marrow suppression secondary to direct infiltration, various therapies or tumour-associated cytokine production (so-called anemia of chronic disease, infection or inflammation) is exceedingly common. However, cancer patients may also experience any of the other possible underlying etiologies. Given the numerous possible causes for anemia associated with malignancy, it is important to consider a systematic approach.

Figure 1 summarizes an approach to investigation.

SEQUENTIAL INVESTIGATION OF ANEMIA IN CANCER PATIENTS

• Direct bone marrow involvement by malignancy frequently alters the marrow sinusoidal matrix, facilitating the release of immature red and white blood cell precursors and producing a leukoerythroblastic blood film.
• Providing the blood film is not grossly abnormal, key first steps involve looking at the combination of the reticulocyte count and mean corpuscular volume (MCV).
• When the reticulocyte count is normal or low, consideration of the major diagnostic possibilities based on the MCV allows a logical approach to the likely diagnosis.

Initial low or normal reticulocyte count: likely diagnosis based on the MCV

• In the case of microcytic anemia, the most common differential diagnosis lies between iron deficiency and thalassemia; beta-thalassemia is more common in people of Mediterranean ancestry while alpha-thalassemia is more frequent in people of Asian background. The single-gene deletion alpha-thalassemia cannot be diagnosed by hemoglobin electrophoresis and has normal hemoglobin (Hb) A2 levels; genetic studies may be required. Unless proven concurrent iron deficiency exists, the microcytosis of thalassemia should not be treated with iron supplements, as iron overload may ultimately result.
• In the case of normocytic anemia, once secondary causes have been ruled out, the anemia of chronic inflammation/infection/malignancy secondary to tumour cytokine production is the most likely diagnosis. However, both ferritin and serum iron/total iron binding capacity may be unreliable in the face of inflammation. The gold standard remains a demonstration of increased or normal iron stores on bone marrow aspiration. The possibility of ongoing occult blood loss should always be ruled out by checking stools for occult blood on at least 3-6 different specimens.
• In the case of macrocytic anemia in cancer patients, vitamin B12 and folate deficiency are reasonably rare compared to chemotherapy- or other drug-induced macrocytosis or underlying myelodysplasia. To confirm a diagnosis of myelodysplasia, bone marrow aspiration/biopsy with flow cytometry and cytogenetics are mandatory. If this diagnosis
**FIGURE 1. Cancer-related anemia: approach to evaluation**

- CBC with MCV and reticulocyte count; review blood smear
- Worrisome findings on peripheral smear?

**Reticulocyte count normal or low**

- **Low MCV**
  - Major considerations: iron deficiency/bleeding, thalassemia, anemia of chronic inflammation (if MCV mildly low)

  - Review old blood cell counts; measure ferritin, serum iron/total iron binding capacity

  - Inconclusive

  - Hemoglobin electrophoresis and Hba2 (rule out beta-thalassemia)
  - Gold standard: bone marrow aspirate and biopsy (evaluate iron stores, rule out marrow infiltrative process)

  - Normal B12, folate
    - Rule out liver disease, occult alcoholism, myelodysplasia (latter requires BM aspirate and biopsy with cytogenetics and flow cytometry)

  - Low B12
    - Evaluate for malabsorption and pernicious anemia

**Normal MCV**

- Major considerations: anemia of chronic liver disease, renal insufficiency, thyroid disease, malignancy, early iron deficiency, blood loss

- Ferritin, serum creatinine, thyroid and liver function tests, serum electrophoresis

  - Inconclusive

- Gold standard: bone marrow aspirate and biopsy (evaluate iron stores, marrow cellularity, rule out marrow infiltrative process)

- Elevated MCV

  - Major considerations: vitamin B12/folate deficiency, chemo or drug effect, alcohol abuse, liver/thyroid disease or myelodysplasia

  - If not obvious from history — measure vitamin B12 and folate

**Reticulocyte count increased**

- Major consideration: blood loss, response of marrow to missing nutrient (iron, folate, B12) or hemolysis

- Check indirect bilirubin, Autoimmune hemolytic anemia (LDH), haptoglobin, Coombs test

- Signs of hemolysis

  - Coombs test

    - Positive
      - IgG + C3d
      - Warm AIHA

    - Negative
      - C3d
      - Cold AIHA

- Other tests as appropriate:
  - cold agglutinins, osmotic fragility (hereditary spherocytosis), G6PD screen (especially if precipitated by drug, acute illness), hemoglobin electrophoresis, Heinz body preparation, hemoglobin electrophoresis, PNH and fragmentation hemolysis investigation

  - Bone marrow examination if findings will change management

  - Consider bone marrow examination if findings will change management

  - Treat as indicated

- No signs of hemolysis

  - Rule out recent blood loss or recent treatment with iron, B12, folate

  - IgG ± C3d
  - Warm AIHA

  - Cold AIHA

  - Bone marrow examination, immune fixation, immunoglobulins

  - Other tests as appropriate:
    - cold agglutinins, osmotic fragility (hereditary spherocytosis), G6PD screen (especially if precipitated by drug, acute illness), hemoglobin electrophoresis, Heinz body preparation, hemoglobin electrophoresis, PNH and fragmentation hemolysis investigation

MCH=mean corpuscular height; RBC=reticulocyte count; CBC=complete blood count; AIHA=autoimmune hemolytic anemia; PNH=paroxysmal nocturnal hemoglobinuria; LDH=lactate dehydrogenase; BM=bone marrow; CT=computed tomography; G6PD=glucose-6-phosphate dehydrogenase; ANA=antinuclear antibodies

© 2012 Parkhurst, publisher of Oncology exchange. All rights reserved.
is a possibility, it is vital to remember to order these tests in advance, to avoid the necessity for a repeat marrow.

**Initial elevated reticulocyte count: likely diagnosis based on presence or absence of hemolysis**
- It is important to remember that there are only 3 causes for an elevated reticulocyte count: acute blood loss, response of the bone marrow to a previously missing nutrient (iron, vitamin B12, folate) or after myelosuppressive drug hemolysis.
- Besides producing a reticulocytosis, hemolysis will usually result in some combination of elevated indirect bilirubin, low haptoglobin, elevated lactate dehydrogenase (LDH) and positive Coombs test (if autoimmune in nature).

**Hemolysis present, Coombs test negative: possible diagnosis**
- The differential diagnosis includes abnormalities of the red cell membrane, red cell enzymes or hemoglobinopathy. Rarer causes include the fragmentation hemolysis syndromes.

**Hemolysis present, Coombs test positive, possible diagnosis depending on specific Coombs antisera results**
- IgG and complement present = warm-type autoimmune hemolytic anemia (AIHA). This may be idiopathic or secondary to underlying lymphoproliferative malignancy (i.e. chronic lymphocytic leukemia [CLL], non-Hodgkin’s lymphoma [NHL] or collagen vascular disease).
- Complement only present = cold-type AIHA or cold agglutinin disease. This may be idiopathic, due to infection (mononucleosis or mycoplasma pneumonia), or secondary to underlying lymphoproliferative malignancy.

**Management of Anemia in Cancer Patients**

**General approach**
- A number of cancer patient studies have shown that the use of erythropoiesis-stimulating agents (ESAs) such as erythropoietin increase hemoglobin levels, decrease transfusion requirements and may improve quality of life.
- Despite this, several studies have reported an increased risk of thromboembolic events and possibly increased mortality from increased cancer progression with ESA therapy.
- To date, no study has shown increased mortality when target levels for hemoglobin were <120 g/L in patients receiving anticancer treatment. Thus, use should be discouraged in patients not on active therapy or with hemoglobin >100 g/L.
- For patients with nonmyeloid malignancies undergoing treatment for cure, the use of ESAs remains controversial and is generally not recommended.
- Treatment should be discontinued if there is no response within 2 months, and the goal hemoglobin should be the lowest level required to avoid transfusion.
- Transfusion therapy should be considered in symptomatic anemic patients when their hemoglobin is <80 g/L, although recently a 70 g/L threshold has also been proposed.

**Specific management of autoimmune hemolytic anemia in cancer patients**
- All cases of AIHA should receive daily supplementation with folic acid, 1-5 mg per day.
- Cold AIHA is notoriously refractory to therapy. With an underlying lymphoproliferative disorder, chemotherapy may lessen hemolysis. Steroids are largely ineffective but responses have been reported with rituximab and chemotherapy combinations.
- Warm AIHA often responds initially to steroid therapy but 30–40% of patients ultimately relapse. In relapsed/refractory disease, subsequent splenectomy has been the traditional approach but rituximab therapy can also be utilized either prior to or post splenectomy. Small studies have demonstrated short-term responses. Lesser evidence exists for the use of immunosuppressive agents such as cyclophosphamide, but such agents are frequently effective. For treatment approach to AIHA, see Figure 2.

**FIGURE 2. Treatment of warm AIHA**

- Prednisone 1 mg/kg (60-100 mg/day) + folic acid 1-5 mg/day
- Continue until normalization of Hb and hematocrit
- Slow dose reduction (4-8 weeks)
- Hemolysis still present
- Yes
- Response
- No
- Increase dose to 1.5 mg/kg
- Steroid refractory AIHA
- Repeat failure
- Yes
- Steroids (low dose) rituximab
- Refractory or recurrent
- No
- Rituximab or immunosuppressive agents (for patients not fit for or refusing splenectomy)
- Other immunosuppressants or experimental therapy

© 2012 Parkhurst, publisher of Oncology exchange. All rights reserved.
THROMBOCYTOPENIA IN CANCER PATIENTS

Thrombocytopenia is also common in patients with cancer. The investigation and management of thrombocytopenia is usually straightforward, rarely requiring invasive tests such as bone marrow aspirate and biopsy. An approach to the investigation of thrombocytopenia in cancer is detailed in Figure 3.4

Bone marrow suppression

• The most common cause of thrombocytopenia in oncology is bone marrow suppression from chemotherapy. This is usually seen in combination with reductions in other cell lines, but rarely it may involve only the platelets.5
• Radiation therapy may also produce thrombocytopenia, particularly after large-dose pelvic irradiation, though this is rarely as severe as thrombocytopenia secondary to chemotherapy.6
• Many other drugs may contribute to suppression of megakaryopoiesis, including antibiotics, alcohol, nutritional deficiencies of B12 and folate, and chronic viral infections like human immunodeficiency virus (HIV).

Splenic sequestration

Splenic sequestration with hypersplenism may occur with certain hematologic malignancies or cirrhosis and secondary portal hypertension. This typically produces only moderate thrombocytopenia without bleeding unless additional coagulation abnormalities are also present.4

PLATELET CONSUMPTION/DESTRUCTION ENTITIES

Heparin-induced thrombocytopenia

• Heparin-induced thrombocytopenia (HIT) should be considered with any fall in platelet count during heparin therapy, particularly unfractionated heparin. However, rare cases have also been described with low-molecular-weight heparin (LMWH).2,10
• Four key features for the diagnosis of HIT are termed the 4 Ts: 1) nature or extent of thrombocytopenia, 2) timing, 3) presence of thrombosis and 4) a lack of other cause.4 This mnemonic helps in identifying a high probability of HIT.9
• The thrombocytopenia is moderate with platelets counts falling by 50% from the pre-heparin levels and typically results in counts of 50-80x10⁹/L. Severe thrombocytopenia (<20x10⁹/L) is rare and should suggest an alternate cause. Some patients will even maintain normal platelet counts or counts >100x10⁹/L but still exhibit a 50% reduction from pre-heparin levels, making the diagnosis more difficult.9
• The timing of HIT typically involves a fall in platelets 5–10 days after the initiation of heparin therapy. Rarely, thrombocytopenia may develop more quickly (within hours to a short number of days) following previous exposure to heparin that had resulted in preexisting circulating antibodies.9,10
• When heparin is discontinued, the platelets typically start to rise within 2–3 days and usually normalize in 4–10 days.
• HIT is associated with a very high risk of both arterial and venous thrombosis, so the dyad of thrombosis and thrombocytopenia while on heparin therapy is highly suspicious.

• Figure 4 outlines an approach to the investigation and management of HIT.
• When appropriate clinical suspicion of HIT exists, an enzyme-linked immunosorbent assay (ELISA)-based test should be ordered. This ELISA testing is highly sensitive, so a negative result can rule out HIT if there is only low or intermediate clinical suspicion. However, the combination of frequent false-positive ELISA tests coupled with delays in lab turnaround effectively means that diagnosis and therapy of HIT remains a clinical decision. Functional assays should follow in intermediate-probability patients with a positive ELISA test (to confirm true HIT). These tests are much more specific than ELISA testing.9,10
• Hematology consultation should be sought whenever possible when initiating HIT therapy. However, the newer anti-Xa inhibitor fondaparinux may ultimately replace the traditional direct thrombin inhibitors lepirudin and argatroban and Xa inhibitor danaparoid.9

Thrombotic thrombocytopenic purpura and disseminated intravascular coagulation

• Thrombotic thrombocytopenic purpura (TTP) is a rare cause of decreased platelets but may occur in the setting of disseminated malignancy.11
• TTP presents with microangiopathic hemolytic anemia (anemia and hemolysis with schistocytes), which results in microvascular thromboses possibly causing renal dysfunction, confusion and rarely fever.4
• TTP may be mistaken for disseminated intravascular coagulation (DIC), which presents with similar features but with the addition of coagulation abnormalities (i.e. low platelet count plus several of the following: prolonged prothrombin time [PT] or partial thromboplastin time [PTT], low fibrinogen or elevated D-dimer).12
• Similar to DIC, the treatment of TTP requires initial control of the underlying malignancy. Plasma exchange, while effective in idiopathic TTP, provides little to no benefit in malignancy-associated TTP.
• Unfortunately, the outcome for malignancy-associated TTP is dismal, with few recoveries regardless of treatment.11,12

**Immune thrombocytopenia**
• Immune thrombocytopenia (ITP) is rare with solid tumours but occurs relatively frequently in the case of low-grade lymphoproliferative disorders, particularly chronic lymphocytic leukemia. Figure 5 provides an approach to treatment of acute and refractory ITP.4,13

**Platelet component therapy**
• Platelet transfusions should only be given if there is active bleeding or if platelets are <10x10^9/L. In a 70-kg adult, one platelet pack raises the platelet count >20-30x10^9/L.
• ABO-compatible platelets should be used whenever possible.
• In potential bone marrow transplant (BMT) patients, irradiated cytomegalovirus (CMV)-negative platelets should be used until CMV status is known (donor platelets prior to BMT must be avoided).
• Irradiated platelets are also required for immunocompromised patients for any reason, including those on purine analogs or with a history of stem cell transplantation.
• HLA-matched platelets usually obtained from a single donor should be considered for refractory patients.

**COAGULOPATHOLOGIES IN CANCER PATIENTS**
Abnormal coagulation tests are relatively common laboratory findings with advanced malignancy. These abnormalities may predate the diagnosis or may result from complications of the underlying disease and/or treatment. Coagulation defects may be associated with bleeding manifestations or rarely thrombotic complications. As shown in Figure 6, the initial evaluation of a patient with an abnormal bleeding tendency can be easily investigated with a limited menu of tests. An approach to cancer-related thrombocytopenia was reviewed earlier in Figure 3.4

**Isolated elevation of the PTT**
• An unexpected new finding of an elevated PTT with previously normal results should raise a suspicion of heparin contamination of the blood sample.
• Indwelling central lines are frequently used so a repeat blood draw from a peripheral site may prevent additional investigations or concerns.
• Lupus-type inhibitors are also a common cause of an isolated PTT elevation. Frequently, they are incidentally diagnosed. These inhibitors generally do not result in increased bleeding but paradoxically may cause increased risk for thrombosis.14,15
• While most inherited bleeding disorders are discovered early in life, mild deficiencies of von Willebrands factor, factor VIII and factor IX may present later. These diagnoses may be easily detected by mixing studies that show immediate correction of the PTT. Specific factor deficiencies are treated with factor replacement.4
• Deficiencies of the contact activators of the intrinsic pathway (factor XII, prekallikrein, high-molecular-weight kininogen) will also cause a marked elevation of PTT, but lack a clinical bleeding tendency.
• Acquired inhibitors (most commonly against factor VIII) are rare but often present with life-threatening bleeding. With mixing studies, an inhibitor may be suspected if there is not an immediate correction. The trigger for inhibitor development is unknown. However, older age and underlying malignancy are reported associations. Acquired factor VIII deficiency represents a medical
emergency requiring immediate hematology consultation for factor replacement and immune suppression. In cancer patients on LMWH and 20% on warfarin. Despite trials showing noninferiority for new oral anticoagulants such as rivaroxaban and dabigatran vs warfarin, therapy and/or the duration of active malignancy. Despite current therapeutic recommendations based on historical trial data, most hematologists in Canada feel that, if appropriately dosed, there exist no significant clinical differences among the various LMWH preparations. Several trials have demonstrated a reduction in symptomatic venous thromboembolism (VTE) recurrence with the use of LMWH over warfarin in VTE associated with malignancy. The current standard of care is to treat with LMWH as long as the creatinine clearance is >30 ml/min and to continue LMWH throughout the duration of chemotherapy and/or the duration of active malignancy. Despite trials showing noninferiority for new oral anticoagulants such as rivaroxaban and dabigatran vs warfarin, these medications have never been compared to LMWH in the cancer population, and thus there is no current indication for these agents in this setting. Recurrent clots during treatment can occur in up to 9% of cancer patients on LMWH and 20% on warfarin.

**Isolated elevated PT/International Normalized Ratio (INR) (Figure 6)**

- The most common cause of an elevated INR is anticoagulation with a vitamin K antagonist (warfarin). Nutritional deficiency of vitamin K associated with poor oral intake, general unwellness/hospitalization, severe liver disease or broad-spectrum antibiotic therapy is also common in malignancy.
- When vitamin K replacement (1-5 mg oral or subcutaneously) does not result in correction of the coagulopathy, liver dysfunction should be considered and may represent occult liver metastases.
- Plasma therapy may be used for liver dysfunction-associated bleeding or if there is need for invasive tests or procedures. Vitamin K should also be provided since liver dysfunction and vitamin K deficiency frequently coexist.

**Combined elevation of PTT and PT/INR (Figure 6)**

- DIC is a frequent manifestation of metastatic cancer (particularly adenocarcinoma and acute promyelocytic leukemia) and may present with bleeding or clotting.
- Thrombocytopenia accompanied by very low fibrinogen (less than 1.0) in the setting of combined PTT and PT/INR elevations suggests DIC. This should prompt rapid investigations for metastases and/or infection.
- Cancer-associated DIC carries a poor prognosis especially if treatment cannot remedy the underlying problem.
- Cryoprecipitate or fibrinogen concentrates with platelet therapy may be used to transiently replace fibrinogen/coagulation deficiencies but there is no durable improvement without correction of the underlying disease.
- Both severe liver dysfunction and excessive warfarin anticoagulation may also present with elevations of PT/INR and PTT.

**CANCER-ASSOCIATED THROMBOSIS**

Primary prophylaxis should be offered to all patients hospitalized with active cancer. Primary prophylaxis has also been recommended with specific chemotherapy regimens known to be associated with increased risk of thrombosis. These include the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide in myeloma, with the standard prophylaxis being use of acetylsalicylic acid (ASA) 81 mg PO daily or prophylactic doses of LMWH in patients with a previous history of clots. Such recommendations are not based on quality data and tend to be centre-dependent. No literature exists to support the use of prophylaxis in other circumstances, including the use of bevacizumab, cisplatin or erythropoietin-stimulating agents.

**When and how to use LMWH therapy**

- Despite current therapeutic recommendations based on historical trial data, most hematologists in Canada feel that, if appropriately dosed, there exist no significant clinical differences among the various LMWH preparations.
- Several trials have demonstrated a reduction in symptomatic venous thromboembolism (VTE) recurrence with the use of LMWH over warfarin in VTE associated with malignancy.
- The current standard of care is to treat with LMWH as long as the creatinine clearance is >30 ml/min and to continue LMWH throughout the duration of chemotherapy and/or the duration of active malignancy.
- Despite trials showing noninferiority for new oral anticoagulants such as rivaroxaban and dabigatran vs warfarin, these medications have never been compared to LMWH in the cancer population, and thus there is no current indication for these agents in this setting.
- Recurrent clots during treatment can occur in up to 9% of cancer patients on LMWH and 20% on warfarin.

---

**FIGURE 5. Treatment of acute and refractory ITP**

- If splenectomy contraindicated or persistent platelets <20x10⁹/L post splenectomy:
  - antiCD20 agent (rituximab)
  - thrombopoietin receptor agonists
  - danazol
  - immunosuppression with chemotherapy

- If relapse or require >10 mg prednisone to maintain platelet count, consider splenectomy

- Emergency treatment
  - Patient bleeding — give platelets
  - IV methylprednisolone (1.0 g IV x 1-3 days; doses may vary)
  - IVIG (1.0 g/kg x 2 days)
  - ± anti-D (75 µg/kg) in Rh+ non-splenectomized patients if no response after >7 days and no evidence of hemolysis
  - Tranexamic acid if bleeding/wet purpura

- Initial treatment
  - Consider when platelets <20x10⁹/L and/or bleeding
  - Prednisone 1 mg/kg/day (and vitamin D, calcium, gastric protection) or dexamethasone 40 mg PO once daily x 4 days
  - Consider IVIG if steroids contraindicated or if no steroid response after 14 days or a more rapid increase in platelets required
  - Consider anti-D in Rh+ nonsplenectomized patients with no evidence of hemolysis

- Platelets >30x10⁹/L:
  - Continue steroid taper over >12 weeks
  - Monitor for steroid induced adverse effects
  - If relapse or require >10 mg prednisone to maintain platelet count, consider splenectomy

- Persistent platelets <20x10⁹/L and bleeding
  - Immunization and splenectomy
  - Pneumococcal and meningococcal vaccine every 5 years
  - No further therapy so long as platelets remain >30x10⁹/L

ITP=immune thrombocytopenia; IVIG=intravenous immunoglobulin.
Risk factors for rethrombosis appear to include metastasis, younger age, or VTE within 3 months of cancer diagnosis. When failure occurs on LMWH, possible strategies to optimize dosing include verifying factor Xa levels to ensure therapeutic anticoagulation is present, switching to twice-daily dosing to allow for drug steady state, or increasing LMWH dosing by 25% with an associated minimal increased risk of bleeding.

Management of coagulation issues with venous catheters

Many chemotherapeutic protocols require the insertion of central venous catheters (CVC). While catheter-related thrombosis remains a frequent problem causing significant ongoing difficulties with chemotherapy access, no study has demonstrated clear benefit to prophylactic anticoagulation.

With proven CVC-related clots, LMWH therapy is recommended as long as the catheter is functioning and not infected. With proper anticoagulation, the risk of clot propagation or postthrombotic syndrome appears minimal. With proven CVC-related clots, the duration of anticoagulation post removal is controversial, with 3 months typically recommended based on extrapolated deep vein thrombosis (DVT) literature.

References