Recent therapeutic advances in hematological malignancies: dealing with treatment-related complications

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introduction

The treatment of patients with hematological malignancies can be complicated by substantial toxicities. Most of those affect rapidly dividing tissues such as bone marrow or mucosal cells, but other toxicities such as neuropathy, pain and impairment of emotional and psychological well being may also often be encountered. Due to space limits pain and psychological distress will not be covered in this report.

infections

Patients with hematological malignancies have a significantly increased risk of infections [1], which stems from the immunosuppressive effect of the underlying disease and even more often from therapy-induced neutropenia. Aggressive treatment is often associated with destruction of mucosal barriers and increased penetration of bacteria from the gastrointestinal (GI) and urinary tract. Other risk factors are obliteration or compression of draining structures (ureter, biliary tract), indwelling devices (venous access and catheters) and exposure to infectious agents by therapies [cytomegalovirus (CMV)-infected transfusions] and the hospital environment (insufficient hand sanitation).

The risk of infection increases sharply with the severity and duration of neutropenia. Therapy with higher doses of glucocorticoids or with bortezomib may result in newly acquired or reactivated viral infections and glucocorticoid therapy is frequently associated with oral or esophageal candidosis. A list of bacteria and fungi frequently involved in infection of cancer patients with neutropenic fever is shown in Table 1.

Clinical evaluation of a patient with a suspected infection includes a careful history and physical examination of the skin, sinuses, fundi, oropharynx, lung, abdomen, surgical sites, indwelling catheters and perirectal area. In addition, a complete blood count, blood chemistry profile and blood cultures and, if indicated, for protozoa and viruses (CMV and rotavirus).

Empiric antibiotic treatment with a broad spectrum antibiotic must be started immediately (after blood cultures have been taken) in patients with neutropenic fever. Some neutropenic patients may fail to show fever as a symptom of sepsis; suddenly emerging fatigue and weakness can be the only obvious symptoms of severe infections.

In intermediate- and high-risk patients, monotherapy with a fourth generation cephalosporin such as cefazidim or alternatively, meropenem or imipenem, or combination treatment with an anti-pseudomonas ß-lactam and an aminoglycoside antibiotic is recommended (Figure 1).

Patients at low risk may be started on oral treatment either with a quinolone or macrolide antibiotic or with cefixim, trimethoprim–sulfamethoxazole or amoxicillin–clavulanic acid. Effectiveness of treatment must be monitored and in the case of insufficient results parenteral therapy should be started.

It should be kept in mind that these drugs usually do not provide coverage for coagulase-negative staphylococci, methicillin-resistant Staphylococcus aureus, enterococci, some strains of penicillin-resistant Streptococcus pneumonia and viridans streptococci. In these cases, vancomycin is the treatment of choice [2].

If fever persists after 3 days of antibiotic therapy, the situation should be carefully reassessed and the antibiotic regimen adapted. Vancomycin may be added to cover the Gram-positive spectrum. Amphotericin or one of the new anti-fungals (voriconazole, caspofungin) should be added in high-risk patients with persistent neutropenia and without clinical improvement after 3–6 days of antibiotic therapy.

Antibiotic treatment for patients without significant risk factors should preferably be prescribed as oral medication. Ciprofloxacin is commonly recommended for enteral and urinary tract infections. For pulmonary infections, third generation cephalosporins, macrolides, a combination of amoxicillin–clavulanic acid or quinolones may be used.

Selection of antiviral drugs depends on the viruses involved or suspected. Acyclovir and the newer compounds (famciclovir, valaciclovir) are given for herpetic infections, foscarnet, acyclovir or zidovudine for CMV disease, ribavirin for patients...
infected by respiratory syncytial virus and oseltamivir for infections caused by influenza virus.

**antibiotic prophylaxis**

Several recent studies underline the value of antibiotic prophylaxis in patients treated with cyclic chemotherapy for a variety of cancers. Older studies used various antibiotics including cotrimoxazole and more recent trials mostly quinolones. Antibacterial prophylaxis reduces the frequency of febrile episodes by ~30–50%, the need for hospitalization due to infections, the frequency of episodes of sepsis and, most importantly, mortality. These findings have recently been confirmed by a Cochrane review showing a reduced risk for mortality due to infections [relative risk (RR) 0.58] and also for all cause mortality (RR 0.66) [3]. The only concern with antibiotic prophylaxis relates to the increased risk of antibiotic resistance with their widespread use. Notwithstanding, due to the significant clinical benefits, antibiotic prophylaxis seems to be a valuable choice, especially during the first cycle of chemotherapy. Prophylaxis should definitely be considered in elderly patients and in those at highest risk for infections.

Patients planned to undergo splenectomy should be vaccinated against the encapsulated bacteria pneumoci, meningococi and Haemophilus influenza several weeks before surgery, because such patients are at increased risk for infections with encapsulated bacteria.

Anti-herpetic prophylaxis should be considered in patients at high risk of viral infection or reactivation, such as those treated with glucocorticosteroids or bortezomib.

Oral amphotericin suspension, swallowed four times daily, or oral fluconazole, 50 mg daily may be used for prophylaxis of oro-esophageal candidosis during treatment with glucocorticoids.

**Table 1.** Frequent causes of infections in neutropenic patients with hematologic cancers

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative streptococci</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td>Corynebacteria</td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td></td>
</tr>
<tr>
<td>Aspergillus</td>
<td></td>
</tr>
</tbody>
</table>

**Immediate installment of therapy with**

*Monotherapy:* Cefazidim, Cefepim, Piperacillin+Tazobactom, Imipenem, or Meropenem

*Duo therapy:* Acyclovinicillen, or third/fourth class Cephalosporin each combined with Aminoglycoside

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<table>
<thead>
<tr>
<th>Yes</th>
<th>Clinical Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Yes

Fever after 72-96 hours

No

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Rerevaluate: Chest-Xray, or HRCT,
Blood Cultures

Clinical stable

Yes

No modification

---

After MonoTX: add Aminoglycoside
After Duo TX: add Carbapenem or Chinolon+Glycopeptid

Fever after 72-96hrs

No

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Add Fluconazol or in higher risk:
Amphotericin Voriconazol or Caspofungin

Add Glycopeptide only in case of mucositis or catheter infections

**Figure 1.** Treatment algorithm for standard risk patients with neutropenic fever.
neutropenia

Myeloid growth factors stimulate the proliferation and differentiation of myeloid precursors and shorten leucopenia and reduce the risk of bacterial infections. Presently, a glycosylated (filgrastim) and non-glycosylated (lenograstim) granulocyte-colony stimulating factor (G-CSF) with short half-life and need for daily injections and a pegylated filgrastim (pegfilgrastim) with longer half-life are available for therapy. G-CSFs are indicated for primary or secondary prophylaxis of neutropenia during chemotherapy and for treatment of febrile neutropenia [4].

Primary prophylaxis has been recommended in patients undergoing cancer treatment with a >20% risk of febrile neutropenia and/or in which reduction of chemotherapy dose or increase of treatment interval would jeopardize treatment outcome. Risk factors for the development of febrile neutropenia are given in Table 2.

Primary prophylaxis has been tested in a few studies with dose-dense chemotherapy protocols in patients with aggressive lymphoma, where superiority of a 2-weekly over a 3-weekly scheduled chemotherapy has been shown. It is, however, difficult to predict the development of febrile neutropenia in an individual patient, which is mainly dependent on two factors, namely (i) dose and timing of chemotherapy and (ii) the bone marrow reserve and the biological status of the individual patient. This inability to precisely predict which patient will finally develop febrile neutropenia results in a number-to-treat ratio of 4:1, meaning that four patients need to receive G-CSF prophylaxis in order to avoid a single episode of febrile neutropenia. In spite of this limitation, the existing evidence shows that prophylaxis with G-CSF reduces antibiotic use, hospitalization, is cost efficient and enhances the patient’s quality of life by reducing sequels of infections.

Secondary prophylaxis is recommended in patients who have experienced severe febrile neutropenia during the preceding chemotherapy and where dose reduction would jeopardize outcome.

Limited evidence exists for a possible benefit of treatment in patients with established neutropenic fever. Treatment should be limited to patients with poor risk factors, such as serious co-morbidity, high age and a high likelihood of becoming neutropenic without use of G-CSFs.

<table>
<thead>
<tr>
<th>Patient related</th>
<th>Disease related</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Advanced disease</td>
<td>Dose-intensive chemotherapy</td>
</tr>
<tr>
<td>Poor performance status</td>
<td>Bone marrow involvement</td>
<td>Dose-dense chemotherapy</td>
</tr>
<tr>
<td>Renal or heart disease</td>
<td>Hematological malignancy</td>
<td>Concomitant radiotherapy</td>
</tr>
<tr>
<td>Pre-treatment neutrophil count &lt;1000/ml</td>
<td>Extensive pre-treatment</td>
<td></td>
</tr>
</tbody>
</table>

Patients with either one or more treatment-related risk factor or two or more patient- and/or disease-related risk factors are candidates for primary prophylaxis with granulocyte-colony stimulating factor (G-CSF).

anemia

Anemia is a common complication of hematological malignancy and its treatment. About 40% of European cancer patients present with anemia (hemoglobin <12 g/dl) and the incidence of anemia may be as high as 75–80% depending on the type and dose of chemotherapy, the underlying disease and possible co-morbidities. Cancer therapy, chemo-, radiotherapy and combined modality treatment, may cause anemia or aggravate an already existing anemic state which is frequently due to ‘chronic anemia of cancer’ [5].

Young patients with slow onset of anemia may adjust to anemia and tolerate it quite well, but anemia is usually associated with mild to severe symptoms such as fatigue, weakness, dyspnea, depression, sleeplessness, emotional disturbance or impaired cognitive function. In severe anemia congestive heart failure and pulmonary edema may ensue.

red blood cell transfusion

Transfusion of one to several volumes of red blood cells has been the traditional approach to patients with symptomatic anemia before introduction of erythropoietins and is still indicated in cases where a rapid increase in circulating red cell mass is needed. One unit of red cells consists of ~1.7 × 10^{12} red cells in 270 ml, 0.2 × 10^9 platelets and 200–250 mg iron. Nowadays, special filters that reduce contamination with white blood cells are applied to reduce the risk of allo-immunization, transfusion reactions and of transferring CMV infections [6].

Transfusions offer the advantage of an immediate increase in hemoglobin, but several factors limit their usefulness. Their effect is only transient, the supply of packed red blood cells is limited, transfusions bear the risk of acute and of late transfusion reactions, infections, iron and volume overload, and of cardiac congestion due to white blood cell aggregation in the pulmonary circulation.

Randomized trials revealed a negative impact of peri-operative transfusions on survival in patients subjected to surgery due to colorectal cancer [7]. Hence, transfusions should be limited to patients with significant symptoms from anemia and the need for fast relief. The recommended trigger value for transfusion is a hemoglobin level of ≤8.0 g/dl. Transfusions must be irradiated before administration to severely immunosuppressed patients (such as allo-transplanted patients and extensively treated Hodgkin’s disease) in order to inhibit the replicative potential of immunocompetent donor lymphocytes and to prevent graft versus host disease.

erthropoietin stimulating agents

Erythropoetin is the most important stimulator of red blood cell production. It enhances proliferation, inhibits apoptosis of red cell precursors, and induces hemoglobin synthesis. Presently, erythropoetin α, erythropoetin β, erythropoetin ζ and darbepoetin α are available for clinical use. The first three consist of an amino acid backbone of 165 amino acids and three carbohydrate side chains. Darbepoetin also consists of 165 amino acids (of which six have been exchanged) but has in
Red blood cell transfusions are recommended in severely symptomatic patients. Discontinue treatment with erythropoietins if patients responding to erythropoietin enjoy improved physical activity, cognitive function and overall quality of life, although a significant improvement had not been confirmed in all studies.

An important side-effect of ESA therapy has only lately become clear. ESAs may induce excess mortality when given to patients outside the presently approved indications. This has now been shown in eight randomized trials, all of them showing increased mortality in the ESA arm. A recent meta-analysis of 51 trials [10] revealed a 10% increase in mortality in patients treated with ESAs compared with controls. Presently, it is unclear whether greater tumor progression and/or thromboembolic complications account for these alarming sequels of ESA therapy. Hence, it has been decided by the US Food and Drug Administration (FDA) to subject all available evidence to rigorous review and to conduct a meta-analysis based on individual patient data.

### Nausea and emesis

Nausea and emesis (N/E) are frequent complications of cancer and cancer therapy. Chemotherapy- and radiotherapy-induced nausea and emesis is classified as acute, delayed or anticipatory N/E. Acute N/E is induced mainly by the release of 5-hydroxytryptamine (5-HT) from chromaffin cells of the GI tract and manifests while patients receive chemotherapy or shortly thereafter (within the first 24 h). It can be subdivided into acute (within 12 h) and sub-acute (12–24 h) N/E. Delayed N/E manifests after ≥24 h after chemotherapy and may persist for 5–7 days. Anticipatory N/E is defined as a symptom that occurs after an initial experience with chemotherapy and is due to inappropriate conditioning of specific reflexes. Its incidence increases with the duration of chemotherapy. Besides treatment-induced N/E (which includes opioid-induced N/E), other factors, such as liver involvement by tumor, other GI causes and central nervous system (CNS) involvement may account for N/E [11].

The intensity of chemotherapy-induced N/E depends greatly on the type of cytostatic drug and the dose used. Other important risk factors are specific polymorphisms of cytochrome P450 that account for variations in the degradation of 5-HT3 receptor antagonists, young age, female gender,

### Table 3. Cancer- or chemotherapy-induced anemia

<table>
<thead>
<tr>
<th>Start treatment with erythropoietins</th>
<th>ASCO/ASH: Hb ≤10 g/dl; EORTC: Hb 9–11 g/dl&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin &lt;i&gt;α&lt;/i&gt; or &lt;i&gt;β&lt;/i&gt;, or &lt;i&gt;ζ&lt;/i&gt;, darbepoetin</td>
<td>10 000 IU, 3x per week or 30–40 000 IU once weekly, or alternatively, with darbepoetin 150 mg once weekly or 500 mg every 3 weeks (Table 3). Hemoglobin should be increased to a target concentration of 12 g/dl according to the American and to 12–13 g/dl according to the European guidelines. In cases of no response after 4 weeks, an increase in the dose by 50% will only result in an additional 10–20% responses. Treatment should be discontinued if there is no response after 8 weeks with the exception of patients with MDS, who may respond only after prolonged therapy. Intravenous iron supplementation has been shown to shorten the time to response and possibly also enhance response rate. Prophylactic treatment in non-anemic patients with a high risk of developing anemia can be considered, but is not established as routine procedure. Only 50–70% of patients respond (increase in hemoglobin concentration of ≥2 g/dl) to erythropoietin stimulating agents (ESAs), hence the number of patients needed to treat to avoid transfusions in a single patient is four. Patients responding to erythropoietin enjoy improved physical activity, cognitive function and overall quality of life, although a significant improvement had not been confirmed in all studies.</td>
</tr>
</tbody>
</table>

| Target Hb level | **| |
| In case of insufficient response<sup>b</sup> (increase in Hb <1.0 g/dl within 4 weeks) | **| |
| When target Hb is reached | **| |
| In case of iron deficiency transferrin saturation <25%, and/or <10% hypochromic red cells | **| |
| Discontinue treatment with erythropoietins <8 weeks | **| |

| Red blood cell transfusions are recommended in severely symptomatic patients needing fast increase in Hb or in those without response to erythropoietins. Trigger level for transfusions: Hb ≤ 8.0 g/dl | **| |

<sup>a</sup>Treatment should be started depending on anemia-related symptoms.

<sup>b</sup>Not considered a standard recommendation.

Hb, hemoglobin.
episodes of N/E during previous gravidity or chemotherapy and low alcohol consumption.

Treatment and prophylaxis of N/E has made great progress with the introduction of 5-HT3 receptor antagonists and more recently with the approval of a neurokinin 1 (NK1) receptor antagonist. Previously, dopamine receptor antagonists, such as metoclopramide, alizapride and haloperidol were the only available active anti-emetic drugs, besides dexamethasone [12].

Although the precise mechanism of action of dexamethasone has not been revealed as yet, it is standard treatment of delayed N/E, and is frequently used for other types of N/E often in combination with other drugs. Metoclopramide is the most important dopamine receptor antagonist and is recommended as single agent in low emetogenic chemotherapy regimens. It also exerts pro-kinetic effects and shows a moderate dose–response relationship, partly because high doses also antagonize 5-HT3 receptors. Presently, there are four 5-HT3 receptor antagonists (ondansetron, granisetron, tropisetron and dolasetron) with comparable activity, and palonosetron, a 5-HT3 receptor antagonist with significantly longer half-life, available for treatment. Tolerability is usually very good, with headache and diarrhea as relatively rare side effects. Aprepitant is the first in class NK1 receptor antagonist with excellent CNS penetration, synergistic activity with 5-HT3 receptor antagonists and high activity in cisplatin-induced N/E. Benzodiazepines, particularly lorazepam, enhance the activity of anti-emetics; in addition they induce sedation and emotional distraction and are also recommended for treatment of anticipatory N/E.

Treatment recommendations for acute N/E depend on the emetogenic potential of chemotherapy and patient-specific factors [13]. For low emetogenic treatments, single-agent dexamethasone or metoclopramide may be used. Dexamethasone should be combined with 5-H3 antagonists in patients treated with a moderately emetogenic protocol and aprepitant in combination with 5-HT3 antagonists, dexamethasone and others is recommended for highly emetogenic platinum-based regimens (Table 4). For delayed emesis, single-agent dexamethasone or metoclopramide is recommended. In the case of insufficient control, combination treatment with aprepitant should be considered.

### diarrhea
Diarrhea in patients with cancer is a symptom of injury of the GI mucosal cells caused by cytostatic treatment (particularly irinotecan, bortezomib and high-dose chemotherapy) or radiotherapy. In addition, other harmful microorganisms, the disease itself, physical reactions to diet, laxative regimens and in patients undergoing allogeneic bone marrow transplantation, graft-versus-host disease may account for diarrhea. Symptoms may vary from increased stool frequency with or without cramps, abdominal pain and meteorism to severe and even life-threatening complications such as excessive fluid loss, hypokalemia and sepsis. Treatment should, whenever possible, aim to eliminate or avoid the cause of diarrhea. In the case of suspected infections, fecal examination with tests for the suspected pathogens should be carried out [14].

Symptomatic treatment consists of opioids and in severe cases also of the administration of anti-secretory agents. Loperamide, an opioid receptor agonist of the mu opioid receptors in the myenteric plexus of the large intestine, does not affect the CNS as other opioids do and is the treatment of choice. It works by decreasing the activity of the myenteric plexus, which decreases the motility of the circular and longitudinal smooth muscles of the intestinal wall. Diphenoxylate is another opioid agonist that slows down intestinal contractions and is available in some countries in combination with atropine, a strong inhibitor of GI secretion.

Other anti-secretory agents that may be used include bismuth–subsalicylate and somatostatin, which suppress secretion of gastric acid and pepsin, lowers the rate of gastric emptying, reduces smooth muscle contractions and blood flow within the intestine, and the secretion of gastrointestinal hormones. Somatostatin analogues with prolonged half-life may be particularly active in patients with massive diarrhea due to short bowel syndrome. Rehydration, and, in cases of hypokalemia, electrolyte supplementation, should be considered.

### constipation
Constipation ensues when the colon absorbs too much water or if the colon’s muscle contractions are slow or sluggish, causing

**Table 4.** Risk adapted anti-emetic prophylaxis according to the guidelines of the Multinational Association of Supportive Care in Cancer

<table>
<thead>
<tr>
<th>Risk of emesis</th>
<th>Acute (day 1)</th>
<th>Followed by</th>
<th>Delayed (days 2–5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5-HT3 + Dex + NK1</td>
<td>→</td>
<td>Dex + NK1</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-HT3 + Dex or 5-HT3 + Dex + NK1 (in the case of insufficient activity of a two-drug combination)</td>
<td>→</td>
<td>Dex single agent or 5-HT3 single agent or metoclopramide single agent, or Dex + NK1 in patients with inadequate control</td>
</tr>
<tr>
<td>Low</td>
<td>Dex</td>
<td>→</td>
<td>None</td>
</tr>
<tr>
<td>Minimal</td>
<td>None</td>
<td>→</td>
<td>None</td>
</tr>
</tbody>
</table>

5-HT3, 5-HT3 receptor antagonist; Dex, dexamethasone; NK1, neurokinin-1-receptor antagonist.
the stool to move through the colon too slowly. As a result, stools can become hard and dry. Common causes of constipation in cancer patients can be classified as cancer related, drug related and others, and are listed in Table 5.

Correct diagnosis is a prerequisite for selection of appropriate therapy. Constipation must be distinguished from intestinal occlusion by patient history, physical investigation, and/or radiological and endoscopic procedures. In drug-induced constipation, discontinuation of the etiologically responsible agent is recommended, but may be difficult in patients requiring effective pain treatment with opioids. Transdermal opioids and opium rotation may help to reduce opium-induced constipation [15].

Adequate hydration, increase in fiber intake and physical activity are commonly recommended, but these measures often are not sufficiently effective. Hence, laxatives are frequently prescribed [16].

They can be allocated to different categories as listed in Table 6.

mucositis

Mucositis occurs when chemo- and/or radiotherapy breaks down the rapidly dividing epithelial cells lining the GI tract, particularly in the oral cavity, leaving the mucosal tissue vulnerable to ulceration and infection. Oral mucositis is the most common manifestation, although mucositis can occur anywhere along the digestive tract from the mouth to the anus. The ensuing damage may include the shedding of the outer mucosal layer, breaks and holes (ulcers) in the skin layers and a general wasting of the tissues [17].

In addition, patients undergoing chemotherapy or radiation therapy are more prone to cuts, nicks and lacerations caused by chewing because of their compromised mucosa. The frequency and localization of mucositis depends on the type and dose of cancer therapy and may be as high as >90% after total body irradiation and high-dose chemotherapy for allogeneic stem cell transplantation.

Mucositis can be mild requiring little intervention, but may also lead to severe pain and other complications. It facilitates the intrusion of microorganisms and is frequently associated with reactivation of herpetic infections and may lead to inability to swallow with consecutive hypovolemia, electrolyte abnormalities and malnutrition.

Decreasing the bacterial load intra-orally by maintaining good oral hygiene and by using antibacterial (chlorhexidine) and antimycotic (amphotericin) mouth rinses (Table 7) can decrease the risk of systemic infections. Local pain treatment with anesthetics (xylocain) and/or systemic pain therapy is frequently required. Keratinocyte growth factor has been introduced for prophylaxis of oral mucositis in patients undergoing stem cell transplantation recently [18].

bleeding

Bleeding complications may be due to imbalances in the plasmatic clotting system, abnormalities of platelet count or...
function and vascular defects, or a combination of these factors. Liver infiltration by leukemia cells can decrease production of clotting factors, and acquired von Willebrand’s disease as well as primary fibrinolysis may occur in association with leukemias apart from disseminated intravascular coagulation (DIC). In rare cases of amyloidosis, factor X will bind to amyloid fibrils leading to factor X deficiency. Thrombocytopenia can occur as complication of the underlying hematological malignancy or of chemotherapy, and also, albeit less frequently, due to immune-mediated thrombocytopenia. Abnormal platelet function is common in patients with myeloproliferative disorders, particularly in those with polycythemia vera. Paraproteinemia may lead to platelet coating and impaired platelet aggregation.

Symptoms depend on the extent of the bleeding disorder and may consist of epistaxis, hematuria, GI bleeding, petechiae or cerebral bleeding with headache and visual disturbances [19].

Treatment consists of correcting the underlying cause if possible. Platelet transfusions are indicated in patients with platelet counts <10 000 as a prophylactic measure and in those with platelets between 10 000 and 20 000 and overt bleeding. Treatment for patients with coagulopathy consists of infusion of fresh frozen plasma, prothrombin complex, anti-thrombin III and fibrinogen concentrate if required. Tranexamic acid and a-aminocaproic acid may be considered in hyperfibrinolytic state in addition to an activated coagulation pathway [20].

Disseminated intravascular coagulation

DIC is characterized by a widespread and ongoing activation of coagulation, leading to fibrin deposition in small vessels and failure of adequate blood supply to various organs. Ongoing activation of the coagulation system, impaired synthesis and increased degradation of coagulation factors result in decreased levels of pro-coagulant proteins, protease inhibitors and platelets. The situation may result in bleeding complications as well as organ failure due to thrombotic occlusion of small vessels. DIC is always secondary to an underlying disorder, is particularly common in patients with pro-myelocytic leukemia but may also occur in patients with sepsis/severe infection, malignancy and in those with other severe diseases. Thrombin generation in DIC is triggered by tissue factor over the extrinsic pathway [20].

Diagnosis is established by the presence of bleeding tendency and/or occurrence of microthrombi, presence of thrombocytopenia, occurrence of fragmented red cells and various changes in coagulation parameters such as reduction of serum levels of the anticoagulant proteins anti-thrombin III and protein C. Fibrinolytic activity is suppressed, with a sustained increase in plasma levels of plasminogen activator inhibitor type 1 (PAI-1). High plasma levels of PAI-1 are strong predictors of mortality in patients with DIC. A distinct form of DIC can be encountered in acute promyelocytic leukemia, which is characterized by a severe hyperfibrinolytic state in addition to an activated coagulation system. Cerebral hemorrhage can frequently be seen in these patients.

Treatment of DIC focuses on the underlying disorder. If this is successfully treated, DIC may resolve spontaneously. Plasma or platelet substitutions should be avoided, and restricted to patients with active bleeding. The use of anticoagulants is controversial however, in case of overt thrombo-embolism or thrombotic organ damage, administration of therapeutic doses of heparin is clearly necessary. Supplementation of anti-thrombin III and activated protein C has been shown to be beneficial in the setting of DIC.

Disclosures

No significant relationships.

References