I. Background

- The criteria for initiating treatment of relapsed/refractory (R/R) CLL are formalized in the IWCLL guidelines (Hallek et al., 2008).
- Generally, indications to initiate salvage treatment include progressive symptoms associated with active disease, such as night sweats, fatigue, unintentional weight loss, and fever without evidence of infection.
- Progressive anemia (Rai stage III) and thrombocytopenia (Rai stage IV) are also indications for treatment.
- There is no specific lymphocyte count that indicates need for treatment.
- Observation and monitoring are indicated in the absence of indications for treatment.
- For relapsed patients who need treatment, prior treatment, presence of del(17p) or mutated TP53, and age are the most important features that direct subsequent therapy.

II. Therapies for the Management of Relapsed/Refractory CLL

A. Ibrutinib

- The treatment landscape for R/R CLL is changing due to the approval of the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib in 2014.
- Currently, most R/R patients receive first-line chemoimmunotherapy (CIT); therefore, BCR signaling pathway inhibitors (BTK inhibitors and PI3 kinase inhibitors) are their standard salvage regimens.
- The initial phase II trial of ibrutinib that led to accelerated approval was in relapsed patients with CLL who had a median of 4 prior treatments, most of whom had previously received CIT (Byrd et al., 2013).
  - The overall response rate was 71%, with virtually all responding patients achieving partial remission (PR).
  - There was remarkable disease control; the overall median PFS was not reached with over 3 years of follow up (Coutre et al., 2015).
- Patients with del(17p) were the only subgroup for whom a median PFS could be estimated at 32 months, which was far superior to prior PFS reported for this subgroup treated with CIT (Stilgenbauer et al., 2016).
- A phase III trial (RESONATE) in R/R CLL compared ibrutinib to obinutuzumab monotherapy and clearly showed patients treated with ibrutinib to have superior response rates and significantly longer median PFS (not reached) versus those treated with ofatumumab monotherapy (median PFS 8 months; Byrd et al., 2014).
- The most commonly occurring (≥20%) adverse events (AEs) in CLL/SLL patients were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia, and hemorrhage.
- For patients who receive first-line BTK inhibitor therapy, current salvage treatment options include PI3 kinase inhibitor-based treatment (idelalisib), venetoclax, lenalidomide ± CD20 monoclonal antibody (mAb), or CIT (FCR or BR).

B. Idelalisib

- Idelalisib is an oral PI3K delta inhibitor that was approved in combination with rituximab in 2014 for the treatment of relapsed CLL based on a randomized trial comparing this combination to rituximab plus placebo (Furman et al., 2014).
  - Idelalisib and rituximab produced significantly higher response rates and longer PFS (median PFS NR vs 5.5 months), as well as a survival advantage (OS at 12 months 92% vs 80%).
  - As with BTK inhibitors, most responses were PRs.
  - The most common AEs (≥20%) were diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.
C. Venetoclax

Venetoclax is an orally bioavailable small molecule inhibitor of Bcl-2 (Roberts et al., 2016) that functions as a BH-3 mimetic and potently induces CLL cell apoptosis.

Monotherapy is highly effective, including in very high-risk patients with relapsed/refractory del(17p) CLL, for whom it was FDA-approved in 2016 (Stilgenbauer et al., 2016)

- The ORR in this group was 79%, with 8% CR
- The estimated 12-month progression-free survival was 72% and overall survival was 87%
- Venetoclax was safely combined with rituximab and showed high response rate, with durable remissions in relapsed CLL, and is being studied in phase III clinical trial as first-line therapy with obinutuzumab
- Venetoclax is a highly potent inducer of CLL cell apoptosis, accounting for the most notable toxicity of tumor lysis syndrome (TLS) that occurs if patients are started at too high a dose, or if they dose-escalate too rapidly
- Therefore, patients are started at a low daily dose of 20 mg, and escalated weekly over 5 weeks, to the target 400 mg daily to mitigate significant TLS risk
- Even with this strategy, patients at high-risk for TLS by virtue of having bulky lymph nodes and high leukemia count, must be aggressively hydrated prior to and during initiation and escalation and closely monitored
- Toxicities associated with long-term use were mild and included gastrointestinal intolerance and neutropenia (Roberts et al., 2016)

D. Immune-modulating agents

Immune-modulating agents (IMID) such as thalidomide and lenalidomide are currently approved for treatment of multiple myeloma, mantle cell lymphoma, and myelodysplastic syndrome, and have had limited application in CLL

Lenalidomide inhibits CLL cell proliferation through inhibition of cebelon; it has no suppression and the associated long-term morbidity and mortality of allo SCT

Donor availability, advanced patient age, and associated toxicities limit applicability of this modality in CLL

- A boxed warning alerts healthcare professionals of the following potential fatal and serious adverse reactions: liver toxicity, severe diarrhea or colitis, inflammation of the lungs, and intestinal perforation
- There is limited available data on small molecule inhibitor activity (e.g., ibrutinib, idelalisib) in patients who were previously refractory to another small molecule inhibitor; better efficacy is expected for the alternative agent in patients who discontinued the prior agent for intolerance
- If a previously treated patient develops del(17p) or mutated TP53, treatment options include ibrutinib, venetoclax, and idelalisib; preference of non-chemotherapy-based treatment should be driven by prior exposure to a small molecule inhibitor, and review of the safety profiles

In addition, the advent of BCR signaling pathway inhibitors (e.g., ibrutinib) provide multiple treatment options that afford well-tolerated long-term disease control, making allo SCT a least-desirable option for most patients

Currently, the following relapsed/refractory CLL patient populations are considered high-risk and therefore appropriate for allo SCT: BCR inhibitor-refractory (including those with BTK and/or PLCG2 mutations), complex karyotype, del(17p)/mutated TP53 (who have failed first-line BTK inhibitor), and patients with multiply relapsed and fludarabine-refractory CLL

References


General Management of Anemia in CLL

Amy Goodrich, RN, BSN, MSN, CRNP-AC
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Cancer- and chemotherapy-induced anemia is defined as hemoglobin (Hgb) level of <11 g/dL or >2 g/dL drop below baseline (Table 1). Signs and symptoms include easy fatigue, lethargy, systolic murmur, heart palpitations, shortness of breath, and pallor of the skin and mucous membranes (NCI; NCCN 2017). Anemia in patients with cancer adversely affects quality of life and is associated with reduced overall survival (Calabrich, 2011).

CLL is associated with several etiologies for anemias, including autoimmune anemias such as hemolytic anemia (AIHA) in 7-10% of patients and, more rarely, pure red cell aplasia (PRCA) in <1% of patients with CLL (Table 2). Autoimmune anemias are more frequently seen in patients with unfavorable CLL risk factors, in the setting of disease progression, and with many drugs, most notably, purine analogs (Visco, 2014) (Table 3).

<table>
<thead>
<tr>
<th>Table 1. Criteria for Common Adverse Events: Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia Grade</strong></td>
</tr>
<tr>
<td>Grade 1</td>
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<tr>
<td>Grade 2</td>
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<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
<tr>
<td>Grade 5</td>
</tr>
</tbody>
</table>

Based on CTCAE v. 4.0.

<table>
<thead>
<tr>
<th>Table 2. Autoimmune anemias in CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia (AIHA)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Pure red cell aplasia (PRCA)</td>
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</tbody>
</table>

Rogers, 2016; Mintzer, 2009; Molica, 2016.
Table 3. Anti-neoplastic regimens that cause anemia in CLL

<table>
<thead>
<tr>
<th>Grade</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk (&gt;90% frequency of anemia)</td>
<td>Not seen in clinical practice</td>
</tr>
<tr>
<td>Moderate Risk (30%-90% frequency of anemia)</td>
<td>Bendamustine, Clofarabine, Obinutuzumab + Chlorambucil, Alemtuzumab</td>
</tr>
<tr>
<td>Low Risk (10%-30% frequency of anemia)</td>
<td>Lenalidomide + Rituximab, Ofatumumab, Venetoclax, Idelalisib + Rituximab</td>
</tr>
<tr>
<td>Minimal Risk (&lt;10% frequency of anemia)</td>
<td>Ibrutinib, Fludarabine, cyclophosphamide, rituximab, Rituximab</td>
</tr>
</tbody>
</table>

Table 4. Criteria for Common Adverse Events: Hemolysis

<table>
<thead>
<tr>
<th>Hemolysis Grade</th>
<th>CTCAE Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Laboratory evidence of hemolysis only (DAT; Coombs'; schistocytes; decreased haptoglobin)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Evidence of hemolysis and ≥2 g decrease in Hgb</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Transfusion or medical intervention (e.g., steroids)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention required</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Based on CTCAE v. 4.0.

Table 5. Indication for transfusion due to anemia in patients with cancer

<table>
<thead>
<tr>
<th>Status</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptomatic and without comorbidities</td>
<td>observe</td>
</tr>
<tr>
<td>high risk (decline in Hgb with recent intensive chemotherapy or radiation therapy), OR</td>
<td>periodic reevaluation</td>
</tr>
<tr>
<td>asymptomatic with comorbidities</td>
<td>consider red blood cell transfusion, consider erythropoiesis-stimulating agents</td>
</tr>
<tr>
<td>– cardiac disease</td>
<td></td>
</tr>
<tr>
<td>– chronic pulmonary disease</td>
<td></td>
</tr>
<tr>
<td>– cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>symptomatic</td>
<td>red blood cell transfusion, consider erythropoiesis-stimulating agents</td>
</tr>
<tr>
<td>– sustained tachycardia</td>
<td></td>
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<tr>
<td>– tachypnea</td>
<td></td>
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<tr>
<td>– chest pain</td>
<td></td>
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<tr>
<td>– dyspnea on exertion</td>
<td></td>
</tr>
<tr>
<td>– lightheadedness</td>
<td></td>
</tr>
<tr>
<td>– syncope</td>
<td></td>
</tr>
<tr>
<td>– severe fatigue limiting activities and work</td>
<td></td>
</tr>
</tbody>
</table>
References


Molica S, Polliack A. Autoimmune hemolytic anemia (AIHA) associated with chronic lymphocytic leukemia in the current era of targeted therapy. Leukemia Research 2016;50:31-36


General Management of Diarrhea

Initial management of mild diarrhea:
- Counseling on dietary modifications and ensuring adequate oral hydration
- Dietary modifications include eliminating fiber, lactose from diet for mild diarrhea symptoms
- Avoid greasy, fried, acidic foods
- Discontinue high osmolar food supplements (e.g., Ensure)

Pharmacologic interventions have the highest level of evidence for managing chemotherapy-induced diarrhea.

For grade 1 diarrhea (an increase of <4 stools daily over baseline or mild increase in ostomy output as compared with baseline but not interfering with activities of daily living) and not responding to dietary intervention:
- Initiate loperamide 4 mg following first loose bowel movement and then 2 mg every 4 hours
- Alternatively, patients can be instructed to take 4 mg after initial loose bowel movement and then 2 mg after each subsequent loose bowel movement (ONS, 2014; Benson et al, 2004).

For persistent Grade 1 diarrhea (after 24 hours of loperamide) or Grade 2 diarrhea (increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline; not interfering with activities of daily living):
- Begin high-dose loperamide at an initial dose of 4 mg followed by 2 g every 2 hours and 4 mg every 4 hours at night (Smith et al, 2008)
- Consider diphenoxylate-atropine 1-2 tablets every 6-8 hours

For complicated Grade 2 diarrhea and Grade 3-4 diarrhea (Benson et al, 2004; ONS, 2014), characterized by an increase of 7 stools daily over baseline or a severe increase in ostomy output over baseline:
- Consider hospital admission
- Administer octreotide 100-150 mcg SC every 8 hours or 25-50 mcg/hr intravenously (IV)
- Initiate IV fluids to replace fluids and electrolytes as needed for at least 24 hours
- Initiate total parenteral nutrition (TPN) as indicated
- Initiate antibiotics (if an infectious cause is suspected)
- Perform stool workup (for pathogens), laboratory studies, skin assessment

Criteria for Common Adverse Events and intervention

<table>
<thead>
<tr>
<th>Diarrhea Grade</th>
<th>Definition</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Diarrhea Grade 1 (mild) | • Diarrhea increase of 4 stools per day over baseline  
• Mild increase in ostomy output compared with baseline | Recommend dietary modifications (avoid foods that are high in insoluble fiber and fat and increase the amount of soluble, low-fiber foods) and begin anti-diarrheal agents  
• Increase fluids 3-4 liters/day with added sugar and/or salt to avoid dehydration, hyponatremia, and hypokalemia  
• Try to determine causative link to the diarrhea and keep a food diary |
| Grade 2 (mild-moderate) | Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared with baseline; not interfering with ADL | IV fluids indicated 24 hours and unable to take oral hydration  
Reinforce diet, anti-diarrheal agents |
| Grade 3 (severe) | Increase of ≥7 stools per day over baseline; incontinence; severe increase in ostomy output compared with baseline; interfering with ADL | IV fluids ≥24 hours and hospitalization  
Administer octreotide  
Antibiotics (if infection suspected) |
| Grade 4 | Life-threatening consequences (e.g., hemodynamic collapse) | |

CTCAE v. 4.0; Benson et al., 2004; Walko & Grande, 2014.
For patients experiencing significant diarrhea, consider holding antineoplastics until complete resolution of symptoms for at least 24 hours without antidiarrheal therapy and refer to package insert for specific dose management recommendations.

**Dose Modification Guidelines for CLL/SLL**

- Many targeted agents can cause diarrhea and/or colitis. Dose modifications are at the discretion of the treating provider based on package insert and diarrhea severity.
- Newer agents of interest:
  - Idelalisib: Black box warning of fatal and/or serious and severe diarrhea or colitis (Grade 3-5) in 14%-19% of patients. Interrupt and dose reduce or discontinue idelalisib (Zydelig package insert, 2016; Brown et al., 2014).  
  - Ibrutinib: 48%-59% incidence of diarrhea at any Grade with 4% Grade 3-4 (Imbuvica package insert, 2016). Treat as above.  
  - Venetoclax: 35% incidence of diarrhea at any Grade with < 1% Grade 3-4 (Venclexta package insert, 2016). Treat as above.

**References**


General Management of Fatigue

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (NCCN, 2016).

**Grade 1 fatigue** (relieved by rest):
- Monitor fatigue levels
- Energy conservation
  - Set priorities and realistic expectations
  - Pace activities
  - Recognize peaks and schedule activities accordingly
  - Limit napping to maximize night-time sleep quality
  - Structured daily routine
  - Avoid multi-tasking
- Distraction strategies
  - Games
  - Music
  - Social interaction
- Help patient find meaning in current situation

**Grade 2 or 3 fatigue** (not relieved by rest and limiting instrumental or self-care activities of daily living [ADL]):

In patients with CLL/SLL, Grade 2 or 3 fatigue (unable to carry out any work activities, active 50% or less of waking hours) is an indication for treatment (Oken, et al., 1982; Hallek, et al., 2008).

- CLL/SLL disease/active treatment assessment. Fatigue is a common symptom of progressive CLL/SLL and also often an expected side effect of many therapies.
- If not attributable to progressive disease or current treatment, consider other etiologies
  - Anemia not attributable to CLL/SLL or treatment or autoimmune anemia

**Fatigue definition and interventions**

<table>
<thead>
<tr>
<th>Fatigue Grade</th>
<th>Severity on 0-10 scale</th>
<th>CTCAE Definition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue absent</td>
<td>No fatigue = 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>Mild = 1-3</td>
<td>Relieved by rest</td>
<td>Monitor, energy conservation, distraction strategies</td>
</tr>
<tr>
<td>Grade 2 (mild-moderate)</td>
<td>Moderate = 4-6</td>
<td>Not relieved by rest; limiting instrumental ADL</td>
<td>Consider CLL/SLL and/or treatment-related causes and other etiologies</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Severe = 7-10</td>
<td>Not relieved by rest; limiting self-care ADL</td>
<td>Consider CLL/SLL and/or treatment-related causes and other etiologies</td>
</tr>
</tbody>
</table>

CTCAE v. 4.03, 2009; Butt Z., et al., 2008; Hallek M., et al., 2008.
- Nutritional consultation
- Sleep restriction, sleep hygiene, stimulus control
- Bright white light therapy
- Pharmacologic
  - Psychostimulants (methylphenidate)
  - Treatment for pain, emotional distress, or anemia
  - Optimize treatment for sleep dysfunction, nutritional imbalance, and comorbidities

References


General Management of Infection in CLL

Infection is a common issue in CLL/SLL, causing significant morbidity and mortality with an estimated 30-50% of deaths being related to infection. Infection is most commonly therapy-related (long- or short-term toxicity) or disease-related (bone marrow involvement or hypogammaglobulinemia). Therefore, the focus of infection management in patients with CLL/SLL is on prevention of infection (Table 1) and management of hypogammaglobulinemia.

Prevention of infection in CLL

Evaluate infection risk of febrile neutropenia (Table 2) upon instituting therapy and administer myeloid growth factors per recommendations (NCCN, 2016; Sanchez-Ramon, 2016) based on:

- Disease factors
- Regimen (Table 3)
- Patient risk factors
  - Prior chemotherapy or radiation therapy
  - Persistent neutropenia

Management of hypogammaglobulinemia in CLL/SLL

IgG replacement is recommended in the setting of CLL (Sanchez-Ramon, 2016):

- Serum IgG levels <400 mg/dL AND
- Recurrent bacterial infections evidenced by
  - Failure of prophylactic antibiotics OR
  - Severe infections requiring IV antibiotics or hospitalization

Table 1. Risk assessment and anti-infective prophylaxis recommendations when initiating therapy

<table>
<thead>
<tr>
<th>Risk</th>
<th>Disease/Therapy examples</th>
<th>Fever and neutropenia risk</th>
<th>Antimicrobial prophylaxis</th>
</tr>
</thead>
</table>
| Low   |  • Standard regimens for most solid tumors  
      • Anticipated neutropenia less than 7 days                                         | Low incidence             |  • Bacterial: None                                     |
|       |                                                                                       |                            |  • Fungal: None                                       |
|       |                                                                                       |                            |  • Viral: None unless prior HSV episode                |
| Medium|  • Autologous hematopoietic cell transplant  
      • Lymphoma  
      • Multiple myeloma  
      • CLL/SLL  
      • Purine analog therapy  
      • Anticipated neutropenia 7-10 days                                                | Usually high incidence with potential for significant variability |  • Bacterial: Consider fluoroquinolone  
|       |                                                                                       |                            |  • Fungal: Consider prophylaxis during neutropenia and if mucositis anticipated, and consider PCP prophylaxis  
|       |                                                                                       |                            |  • Viral: Use during neutropenia and longer based on risk |
| High  |  • Allogeneic hematopoietic cell transplant  
      • Acute leukemia induction or consolidation  
      • Alemtuzumab therapy  
      • GVHD treated with over 20 mg steroids daily  
      • Anticipated neutropenia over 10 days                                               | Usually high incidence with potential for significant variability |  • Bacterial: Consider fluoroquinolone  
|       |                                                                                       |                            |  • Fungal: Consider prophylaxis during neutropenia and consider PCP prophylaxis  
|       |                                                                                       |                            |  • Viral: Use during neutropenia and longer based on risk |

CTCAE v. 4.03, 2009; Butt Z., et al., 2008; Hallek M., et al., 2008.

Table 2. Criteria for Common Adverse Events: Febrile Neutropenia

<table>
<thead>
<tr>
<th>Grade</th>
<th>CTCAE Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>—</td>
</tr>
<tr>
<td>Grade 2</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3</td>
<td>ANC &lt;1000/mm³ with a single temperature of &gt;38.3°C (101°F) or a sustained temperature of ≥38.0°C (100.4°F) for more than one hour</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention required</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

CTCAE v. 4.0, 2009.
Table 3. Anti-neoplastic regimens associated with neutropenia in CLL

<table>
<thead>
<tr>
<th>High Risk (&gt;90% frequency of neutropenia)</th>
<th>Moderate Risk (30%-90% frequency of neutropenia)</th>
<th>Low Risk (10%-30% frequency of neutropenia)</th>
<th>Minimal Risk (&lt;10% frequency of neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
<td>• Ibrutinib + rituximab</td>
<td>• Ofatumumab</td>
<td>• Ibrutinib + rituximab</td>
</tr>
<tr>
<td>• Ibrutinib</td>
<td>• Idelalisib + rituximab</td>
<td>• Lenalidomide</td>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td>• Lenalidomide + rituximab</td>
<td>• Lenalidomide + chlorambucil</td>
<td>• Rituximab</td>
<td>• Lenalidomide + chlorambucil</td>
</tr>
<tr>
<td>• Obinutuzumab + chlorambucil</td>
<td>• Obinutuzumab + alemtuzumab + bendamustine</td>
<td>• Venetoclax</td>
<td>• Obinutuzumab + chlorambucil</td>
</tr>
<tr>
<td>• Alemtuzumab + bendamustine</td>
<td></td>
<td></td>
<td>• Alemtuzumab + bendamustine</td>
</tr>
</tbody>
</table>


References


General Management of Infusion-Related Toxicity

The most common infusion reactions in patients with CLL/SLL occur during monoclonal antibody infusions and are most commonly infusion- or cytokine release syndrome-related (non-IgE-mediated reactions), although true allergic (IgE-mediated) and anaphylactic reactions are possible. The four infusion reaction types overlap significantly in presentation and management. However, for the purpose of this section, the more common non-IgE-mediated infusion reactions will be the focus. Follow site-specific anaphylaxis protocols for allergic/anaphylactic reactions (Vogel, 2010).

Risk factors for infusion reactions during monoclonal antibody administration (Vogel, 2010; Breslin, 2007; Gobel, 2005; Kimby, 2005):

- Asthma
- Allergies (hay fever, skin irritations, iodine, seafood, drugs)
- Absolute lymphocyte counts of 25K/mm$^3$ or higher
- B-adrenergic blocker therapy
- Autoimmune disease
- Female
- Drug doses above standard
- Initial therapy
- Older age
- Hematologic malignancy
- History of infusion reaction
- Preexisting cardiac or pulmonary dysfunction

Management of infusion reactions/cytokine release syndrome:

Once an infusion-related toxicity is noted, general nursing interventions include:

- Stop infusion and clamp tubing closest to the patient
- Call for help
- Notify prescriber

- Assess using ABC principles (airway, breathing, circulation)
- If possible, relocate patient to a stretcher or medical bay
- Place in supine position with legs raised unless respiratory status is compromised
- Full symptom assessment

Grade 1 (mild) reactions:

- Signs and symptoms include
  - Chills
  - Fever <38° C
  - Transient flushing
  - Mild hypotension (<20% difference from baseline)
  - Pruritus
  - Nausea
  - Rhinitis

  If signs and symptoms are present,
  - Consider diphenhydramine and H$_2$ blocker
  - Place on continuous pulse oximetry
  - Obtain vital signs every 15 minutes
  - If symptoms worsen or persist for >30 minutes, consider IV steroid bolus
  - If symptoms resolve or improve, determine patient disposition and consider re-initiation of infusion

Grade 2 (moderate) reactions:

- Signs and symptoms include:
  - Dyspnea
  - Fever 38.0-38.9° C
  - Persistent flushing
  - Rash
  - Rigors
  - Heart rate >110 bpm
  - Urticaria
  - Vomiting

Premedications to minimize monoclonal antibody infusion-related toxicity in CLL/SLL

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Recommended Premedications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>- Acetaminophen 500-1000 mg 30 minutes prior to first infusion and at each dose escalation</td>
</tr>
<tr>
<td></td>
<td>- Diphenhydramine 50 mg 30 minutes prior to first infusion and at each dose escalation</td>
</tr>
<tr>
<td>Rituximab</td>
<td>- Acetaminophen 1000 mg</td>
</tr>
<tr>
<td></td>
<td>- Antihistamine</td>
</tr>
<tr>
<td></td>
<td>- Corticosteroid</td>
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<tr>
<td></td>
<td>- If receiving a glucocorticoid as part of chemotherapy regimen, administer prior to first infusion</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>- Acetaminophen 1000 mg</td>
</tr>
<tr>
<td></td>
<td>- Antihistamine</td>
</tr>
<tr>
<td></td>
<td>- Corticosteroid</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>- Acetaminophen 1000 mg</td>
</tr>
<tr>
<td></td>
<td>- Antihistamine</td>
</tr>
<tr>
<td></td>
<td>- Glucocorticoid</td>
</tr>
</tbody>
</table>

If signs and symptoms are present,

- Consider diphenhydramine, H₂ blocker and IV steroid bolus
- Place on continuous pulse oximetry
- Obtain vital signs every 5 minutes
- Make suction and oxygen available at the bedside
- Consider O₂ as needed to maintain SpO₂ <93%
- If symptoms worsen, consider
  - Epinephrine
  - IV fluids
- If symptoms resolve or improve, determine patient disposition and consider re-initiation of infusion

**Grade 3/4 (severe) reactions:**

- Signs and symptoms include:
  - Acute deterioration in mental status
  - Loss of consciousness
  - Angioedema
  - Bronchospasm
  - Cyanosis
  - Diaphoresis
  - Fever >39°C
  - Hoarseness/voice changes
  - Severe hypotension (>20% from baseline or SBP <80 mmHg)
  - SpO₂ <90%
  - Stridor
  - Respiratory rate >24/minute
  - Throat or tongue edema
  - Wheezing
- If signs and symptoms are present,
  - Administer:
    - Epinephrine
    - Diphenhydramine
    - H₂ blocker
    - IV steroid
    - IV fluids
    - Consider albuterol if respiratory symptoms present
- Place on continuous pulse oximetry
- Obtain vital signs every 5 minutes
- Make suction and oxygen available at the bedside
- Administer oxygen to maintain SpO₂ >90%
- Determine patient disposition
- Do not reinitiate infusion

**References**


## Grading of Infusion Reactions (CTCAE 4.03)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>N/A</td>
<td>N/A</td>
<td>- Symptomatic bronchospasm ± urticaria &lt;br&gt; - Parenteral intervention required &lt;br&gt; - Allergy-related edema/angioedema &lt;br&gt; - Hypotension</td>
<td>- Life threatening consequences &lt;br&gt; - Urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td></td>
<td></td>
<td>- Transient flushing or rash with drug fever &lt;38°C &lt;br&gt; - Intervention not indicated</td>
<td>- Prolonged reaction &lt;br&gt; - Recurrence of symptoms after initial improvement &lt;br&gt; - Hospitalization indicated for clinical sequelae (i.e., renal impairment, pulmonary infiltrates)</td>
<td>Death</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td></td>
<td></td>
<td>- Mild, transient reaction &lt;br&gt; - Infusion interruption not indicated &lt;br&gt; - Intervention not indicted</td>
<td>- Prolonged reaction &lt;br&gt; - Recurrence of symptoms after initial improvement &lt;br&gt; - Hospitalization indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td></td>
<td></td>
<td>- Mild reaction &lt;br&gt; - Infusion interruption not indicated &lt;br&gt; - Intervention not indicted</td>
<td>- Prolonged reaction &lt;br&gt; - Recurrence of symptoms after initial improvement &lt;br&gt; - Hospitalization indicated for clinical sequelae (i.e., renal impairment, pulmonary infiltrates)</td>
<td>Death</td>
</tr>
</tbody>
</table>
General Management of Nausea and Vomiting in CLL/SLL

Nausea and vomiting in CLL/SLL are most commonly related to therapy as CLL/SLL carries a low incidence of intestinal involvement or other disease-specific causes (Krishna, 2012; NCCN, 2016). Prevention of therapy-related nausea and vomiting is thus the main focus in patients with CLL/SLL.

Calculating the emetogenicity of multiple-agent chemotherapy/biotherapy regimens (Oncology Nursing Society, 2016)
- List each agent contained within the multiple-agent regimen
- Identify the agent with the highest emetogenic level

<table>
<thead>
<tr>
<th>High Risk (&gt;90% frequency of emesis)</th>
<th>Moderate Risk (30%-90% frequency of emesis)</th>
<th>Low Risk (10%-30% frequency of emesis)</th>
<th>Minimal Risk (&lt;10% frequency of emesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>Ibrutinib</td>
<td>Venetoclax</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Idelalisib</td>
<td></td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Cyclophosphamide –1500 mg/m²</td>
<td>Pentostatin</td>
<td></td>
<td>Fludarabine</td>
</tr>
<tr>
<td>Cytarabine &gt;200 mg/m²</td>
<td></td>
<td></td>
<td>Lenalidomide</td>
</tr>
<tr>
<td>Doxorubicin ≤60 mg/m²</td>
<td></td>
<td></td>
<td>Obinutuzumab</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td>Ofatumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vincristine</td>
</tr>
</tbody>
</table>


Identification of emetic risk of anti-neoplastic agents commonly used in CLL/SLL

For prevention of nausea/vomiting from IV agents with moderate and low risk high-risk emetogenic potential (>90% frequency of emesis)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Days 2, 3, 4</th>
</tr>
</thead>
</table>
| **A: Neurokinin-1 antagonist + 5-HT3 antagonist + Steroid** NK1 antagonist (choose one): |**A:** If aprepitant PO Day 1
• Aprepitant 125 mg PO x 1
• Fosaprepitant 150 mg IV x 1
• Rolapitant 180 mg PO x 1

AND
5-HT3 antagonist
• Dolasetron 100 mg PO x 1
• Granisetron 2 mg PO x 1 or 0.01 mg/kg up to 1 mg IV x 1 or 3.1 mg/24 hr transdermal patch applied 1-2 days prior to Day 1
• Ondansetron 16-24 mg PO x 1 or 8-16 mg IV x 1
• Palonosetron 0.25 mg IV x 1

AND
Steroid
• Dexamethasone 12 mg PO/IV x 1

| B: Netupitant-containing regimen | • Netupitant 300 mg/palonosetron 0.5 mg PO x 1
• Dexamethasone 12 mg PO/IV x 1 |
|----------------------------------|---------------------------------|
| C: Olanzapine-containing regimen | • Olanzapine 10 mg PO
• Palonosetron 0.25 mg IV x 1
• Dexamethasone 20 mg IV x 1 |

| B: | • Dexamethasone 8 mg PO/IV daily on Days 2-4 |
| C: | • Olanzapine 10 mg PO on Days 2-4 |

Evidence-Based Clinical Updates in [Symptom] Management for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia
**For prevention of nausea/vomiting from IV agents with moderate-risk emetogenic potential (30%-90% frequency of emesis)**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Days 2, 3, 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A: 5-HT3 antagonist + Steroid ± NK1 antagonist</strong>&lt;br&gt;5HT-3 antagonist (choose one)&lt;br&gt;• Dolasetron 100 mg PO x 1&lt;br&gt;• Granisetron 2 mg PO x 1 or 0.01 mg/kg up to 1 mg IV x 1&lt;br&gt;• 3.1 mg/24 hr transdermal patch applied 1-2 days prior to Day 1&lt;br&gt;• Ondansetron 16-24 mg PO x 1 or 8-16 mg IV x 1&lt;br&gt;• Palonosetron 0.25 mg IV x 1&lt;br&gt;<strong>AND</strong>&lt;br&gt;Steroid&lt;br&gt;• Dexamethasone 12 mg PO/IV x 1&lt;br&gt;<strong>WITH/WITHOUT</strong>&lt;br&gt;• Aprepitant 125 mg PO x 1&lt;br&gt;• Fosaprepitant 150 mg IV x 1&lt;br&gt;• Rolapitant 180 mg PO x 1</td>
<td><strong>A:</strong>&lt;br&gt;<strong>If no NK1 antagonist given on Day 1:</strong>&lt;br&gt;• Dolasetron 100 mg PO on Days 2 and 3 OR&lt;br&gt;• Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg up to 1 mg IV daily on Days 2 and 3&lt;br&gt;<strong>OR</strong>&lt;br&gt;• Steroid monotherapy with dexamethasone 8 mg PO/IV daily on Days 2 and 3&lt;br&gt;<strong>If NK1 antagonist given on Day 1:</strong>&lt;br&gt;<strong>If aprepitant given on Day 1</strong>&lt;br&gt;• Aprepitant 80 mg PO daily on Days 2 and 3 AND&lt;br&gt;• Dexamethasone 8 mg PO/IV on Days 2 and 3&lt;br&gt;<strong>If fosaprepitant on Day 1</strong>&lt;br&gt;• No further NK1 antagonist ±&lt;br&gt;• Dexamethasone on Days 2 and 3&lt;br&gt;<strong>If rolapitant given on Day 1</strong>&lt;br&gt;• No further NK1 antagonist ±&lt;br&gt;• Dexamethasone on Days 2 and 3</td>
</tr>
<tr>
<td><strong>B: Netupitant-containing regimen</strong>&lt;br&gt;• Netupitant 300 mg/palonosetron 0.5 mg PO x 1&lt;br&gt;• Dexamethasone 12 mg PO/IV x 1</td>
<td><strong>B:</strong>&lt;br&gt;• ± Dexamethasone 8 mg PO/IV daily on Days 2 and 3</td>
</tr>
<tr>
<td><strong>C: Olanzapine-containing regimen</strong>&lt;br&gt;• Olanzapine 10 mg PO&lt;br&gt;• Palonosetron 0.25 mg IV x 1&lt;br&gt;• Dexamethasone 20 mg IV x 1</td>
<td><strong>C:</strong>&lt;br&gt;• Olanzapine 10 mg PO on Days 2 and 3</td>
</tr>
</tbody>
</table>

**For prevention of nausea/vomiting from IV agents with low-risk emetogenic potential (10%-30% frequency of emesis)**

- Start any of the following before antineoplastic therapy and repeat daily for multiday doses
  - Dexamethasone 8-12 mg PO/IV daily
  - Metoclopramide 10-20 mg PO/IV and then every 6 hrs as needed
  - Prochlorperazine 10 mg PO/IV and then every 6 hrs as needed up to 40 mg per day
  - Serotonin (5-HT3) antagonist (choose one)<br>    - Dolasetron 100 mg PO daily<br>    - Granisetron 1-2 mg PO daily<br>    - Ondansetron 8-16 mg PO daily

**For prevention of nausea/vomiting from IV agents with minimal-risk emetogenic potential (<10% frequency of emesis)**

- No routine prophylaxis

**For prevention of nausea/vomiting from oral agents with high- to moderate-risk emetogenic potential (>30% frequency of emesis)**

- Start before chemotherapy and continue daily any of the following:
  - 5-HT3 antagonist (choose one)<br>    - Dolasetron 100 mg PO daily<br>    - Granisetron 1-2 mg PO daily or 3.1 mg/24 hr transdermal patch every 7 days<br>    - Ondansetron 16-24 mg PO daily

**For prevention of nausea/vomiting from oral agents with low- to minimal-risk emetogenic potential (<30% frequency of emesis)**

- Start before chemotherapy and continue daily any of the following:
  - Metoclopramide 10-20 mg PO or every 6 hrs prn
  - Prochlorperazine 10 mg PO and then every 6 hrs prn
  - Haloperidol 1-2 mg PO every 4-6 hrs as needed
  - 5-HT3 antagonist (choose one)<br>    - Dolasetron 100 mg PO daily prn<br>    - Granisetron 1-2 mg PO daily prn<br>    - Ondansetron 8-16 mg PO daily prn
References


General Management of Neutropenia in CLL

Neutropenia in CLL/SLL can be therapy- or disease-related. Disease-related neutropenia is most often due to bone marrow involvement with CLL/SLL and is typically managed by treating the underlying disease. Therefore, the focus of neutropenia management in patients with CLL/SLL is prevention, and specifically, prevention of febrile neutropenia.

Prevention of febrile neutropenia in CLL

Evaluate febrile neutropenia risk (NCCN, 2016):

- Disease factors
- Regimen

<table>
<thead>
<tr>
<th>High risk (&gt;20% risk of febrile neutropenia)</th>
<th>Intermediate risk (10-20% risk of febrile neutropenia)</th>
<th>Low risk (&lt;10% risk of febrile neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis with filgrastim, fligrastim-sndz, tbo-filgrastim, or pegfilgrastim</td>
<td>Consider prophylaxis with filgrastim, fligrastim-sndz, tbo-filgrastim, or pegfilgrastim based on patient risk factors</td>
<td>No prophylaxis</td>
</tr>
</tbody>
</table>

Risk assessment and prophylaxis recommendations when initiating therapy

Anti-neoplastic regimens causing neutropenia in CLL

<table>
<thead>
<tr>
<th>High Risk (&gt;90% frequency of febrile neutropenia)</th>
<th>Moderate risk (30%-90% frequency of febrile neutropenia)</th>
<th>Low risk (10%-30% frequency of febrile neutropenia)</th>
<th>Minimal risk (&lt;10% frequency of febrile neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
<td>• Ibrutinib, Idelalisib + rituximab, Lenalidomide + rituximab, Obinutuzumab + chlorambucil, Alemtuzumab, Bendamustine</td>
<td>• Ofatumumab, Lenalidomide, Rituximab, Venetoclax</td>
<td>• Ibrutinib, Idelalisib + rituximab, Lenalidomide + rituximab, Obinutuzumab + chlorambucil, Alemtuzumab, Bendamustine, Ofatumumab, Lenalidomide, Rituximab, Venetoclax</td>
</tr>
</tbody>
</table>

Criteria for Common Adverse Events: Febrile Neutropenia

<table>
<thead>
<tr>
<th>Febrile Neutropenia Grade</th>
<th>CTCAE Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>—</td>
</tr>
<tr>
<td>Grade 2</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3</td>
<td>ANC &lt;1000/mm³ with a single temperature of &gt;38.3° C (101° F) or a sustained temperature of &gt;38.0° C (100.4° F) for more than one hour</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention required</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>
References


Dermatologic toxicities are common in CLL patients receiving treatment (Table 1) and are often cited as a cause of treatment interruption, dose modification, or treatment cessation (Gordon, 2012; Drilon, 2016).

**General preventative and treatment strategies**

Prophylaxis and management of cancer-related rash depends on the grade (Table 2; Bensadoun, 2013).

Upon initiating treatment:
- Patient education
- Daily moisturizers
- Sun protection

For Grade 1 skin toxicity:
- Daily moisturizers
- Sun protection
- Drug-specific interventions
- Acidic cleanser, emollient and antiseptic soap
- Camouflage

For Grade 2-3 skin toxicity:
- Daily moisturizers
- Sun protection
- Drug-specific interventions
- Acidic cleanser, emollient and antiseptic soap
- Camouflage
- Wound care, as appropriate
- Topical corticosteroids
- Referral to dermatology

For Grade 4 skin toxicity:
- Daily moisturizers
- Sun protection
- Drug-specific interventions
- Acidic cleanser, emollient and antiseptic soap
- Camouflage
- Wound care, as appropriate
- Systemic corticosteroids
- Referral to dermatology

**Table 1. Common Drug-Specific Dermatologic Reactions and Management in CLL/SLL**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence, All Grades (Grade 3/4)</th>
<th>Timing</th>
<th>Exam</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>12 (8)</td>
<td>7-10 days after previous cycle and worsens in severity with each cycle</td>
<td>Erythematous cutaneous papules and plaques ± pruritus</td>
<td>Oral antihistamines Topical emollients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More prevalent on sun-exposed skin</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Early onset: 25 (0)</td>
<td>Not reported</td>
<td>Early onset: 15 days Palpable eruptions, typically pruritic, non-blanching, violaceous papules</td>
<td>Dermatology consult, topical corticosteroids, oral anti-histamines If poor control, consider dose interruption and dose reduction</td>
</tr>
<tr>
<td></td>
<td>Late onset: 16 (0)</td>
<td>Not reported</td>
<td>Late onset: 80 days Non-palpable petechial rash</td>
<td>No intervention</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>26 (7)</td>
<td>Most common in first month of therapy</td>
<td>Maculopapular ± localized urticarial ± pruritus</td>
<td>Topical corticosteroids Oral antihistamines Consider dose interruption</td>
</tr>
<tr>
<td>Idelisib</td>
<td>21 (3)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Carilli, 2014; Malipatil, 2011; Iberri, 2016; Tinsley, 2015; Teva Pharmaceuticals, 2015; Janssen, 2016; Gilead, 2016; Celgene, 2015
Table 2. Criteria for Common Adverse Events: Rash

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acneiform</th>
<th>Maculopapular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Papules and/or pustules covering &lt;10% BSA, ± pruritus or tenderness</td>
<td>Macules/papules covering &lt;10% BSA ± pruritus, burning, tightness</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Papules and/or pustules covering 10-30% BSA ± pruritus or tenderness</td>
<td>Macules/papules covering 10-30% BSA ± pruritus, burning, tightness</td>
</tr>
<tr>
<td></td>
<td>Associated with psychosocial impact</td>
<td>Limits instrumental ADL</td>
</tr>
<tr>
<td></td>
<td>Limits instrumental ADL</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Papules and/or pustules covering &gt;30% BSA ± pruritus or tenderness</td>
<td>Macules/papules covering 10-30% BSA ± pruritus, burning, tightness</td>
</tr>
<tr>
<td></td>
<td>Limits self-care ADL</td>
<td>Limits self-care ADL</td>
</tr>
<tr>
<td></td>
<td>Associated with local superinfection with oral antibiotics indicated</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Papules and/or pustules covering any % BSA ± pruritus or tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limits self-care ADL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated with extensive superinfection with IV antibiotics indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Life-threatening consequences</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

Based on CTCAE v. 4.3. BSA=body surface area; ADL=activities of daily living.

References


General Management of Thrombocytopenia in CLL

Thrombocytopenia is defined as platelet count less than lower limit of normal to 75,000/mm³ (Table 1). Thrombocytopenia in CLL is most commonly disease-related, therapy-related (Table 2), or autoimmune-related. Signs and symptoms include easy or excessive bruising (purpura), petechiae, prolonged bleeding from cuts, bleeding gums, epistaxis, fatigue, unusually heavy menstrual flow, and enlarged spleen or liver. Immune thrombocytopenia (ITP) occurs at a rate of 1-15% in patients with CLL (Visco, 2014; Rodgers, 2016). See Table 3 for indications and recommendations for transfusion due to thrombocytopenia.

Initial evaluation:
- Complete blood count with platelets
- Peripheral blood smear

History and physical exam (Stasi, 2012):
- Family history of thrombocytopenia
- Platelet trend/bleeding manifestations (new onset, chronic, relapsing)
- Autoimmune disorders
- Infections
- Malignancies
- Pregnancy status
- Medications
- Vaccinations
- Recent travel
- Recent transfusion
- Ingestion of alcohol and quinine-containing beverages
- Risk factors for retroviral infections and viral hepatitis

Assess for mechanisms of thrombocytopenia specific to CLL (Stasi, 2012):
- Decreased production
  - Chemotherapy-induced thrombocytopenia
  - Leukemic infiltration of bone marrow
  - Myelodysplastic syndrome
  - Aplastic anemia
- Increased destruction
  - Disseminated intravascular coagulation
- Splenic sequestration
- Hemodilution

Secondary ITP (CLL-associated) is defined as (Visco, 2014):
- Otherwise unexplained reduction in platelet count of at least one-half of baseline and below 100 x 10⁹/L
- Normal or increased megakaryocytes in bone marrow aspirate or biopsy
- Absent or limited splenomegaly
- No cytotoxic treatment in the past month
- Exclusion of all other causes of thrombocytopenia

Treatment of secondary ITP (CLL-associated):
- Corticosteroids
- IV Immunoglobulin G
- Rituximab
- TPO receptor agonists
- Rituximab with chemotherapy

Table 1. Criteria for Common Adverse Events: Thrombocytopenia

<table>
<thead>
<tr>
<th>Anemia Grade</th>
<th>CTCAE Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>&lt; LLN - 75,000/mm³</td>
</tr>
<tr>
<td>Grade 2</td>
<td>&lt; 75,000 - 50,000/mm³</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&lt; 50,000 - 25,000/mm³</td>
</tr>
<tr>
<td>Grade 4</td>
<td>&lt; 25,000/mm³</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Based on CTCAE v. 4.0; LLN=lower limit of normal

Table 2. Anti-neoplastic regimens that cause thrombocytopenia in CLL

<table>
<thead>
<tr>
<th>High Risk (&gt;90% frequency of anemia)</th>
<th>Moderate risk (30%-90% frequency of anemia)</th>
<th>Low risk (10%-30% frequency of anemia)</th>
<th>Minimal risk (&lt;10% frequency of anemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
<td>• Ofatumumab</td>
<td>• Idelalisib + Rituximab</td>
<td>• Rituximab</td>
</tr>
<tr>
<td>• Lenalidomide + Rituximab</td>
<td>• Idealalisib + Rituximab</td>
<td>• Lenalidomide</td>
<td></td>
</tr>
<tr>
<td>• Obinutuzumab + Chlorambucil</td>
<td>• Venetoclax</td>
<td>• Bendamustine</td>
<td></td>
</tr>
<tr>
<td>• Alemtuzumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bendamustine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Byrd, 2014; Furman, 2014; Ferrajoli, 2008; Badoux, 2013; Genentech, 2016; Abbvie, 2016; Lozanski, 2004; Hallek, 2010; Genzyme, 2009; Teva Pharmaceuticals, 2015; Celgene, 2015.
Clinical Setting Transfusion Recommendations

Hospitalized adults with therapy-induced hypoproliferative thrombocytopenia
• Transfuse if platelet count of 10 x 10^9 cells/L or less to reduce risk for spontaneous bleeding

Thrombocytopenic adults having minor surgical procedures
• For central venous catheter placement, transfuse if platelet count <20 x 10^9 cells/L
• For lumbar puncture, transfuse if platelet count <50 x 10^9 cells/L

Thrombocytopenic adults having major elective non-neuraxial surgery
• Transfuse if platelet count <50 x 10^9 cells/L

Thrombocytopenic adults receiving antiplatelet therapy who have intracranial hemorrhage
• Transfuse based on clinical factors, size of bleeding and patient level of consciousness
• For central nervous system surgeries, transfuse if platelet count <80 x 10^9 cells/L

Kaufman, 2015.

References