Managing hematological toxicities with FCR

Tina Crosbie, BSc Pharm, ACPR;1 James Johnston, MD (FRCP);2 Jennifer Daley-Morris, BSc Pharm;3 Marc Geirneart, BSc Pharm2

1The Ottawa Hospital, Ottawa, Ontario; 2CancerCare Manitoba, Winnipeg, Manitoba; 3Stronach Regional Cancer Centre

Medical Writer: Anna Christofides MSc, RD, New Evidence
Background

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, representing approximately 30% of all leukemias.\(^1,2\) Although predominantly characterized by neoplastic B-cells, CLL is clearly distinctive from other leukemic diseases and B-cell tumours.\(^2\) In CLL, an accumulation of abnormal B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen causes overcrowding, suppressing the formation and function of blood and immune cells. In addition, malignant lymphocytes do not function normally, further reducing the body’s ability to fight infection.

Bone marrow infiltration by CLL cells can result in a number of cytopenias, which are predictive of poor prognosis in patients with CLL.\(^2,3\) In addition, CLL is characterized by a high prevalence of autoimmune disease such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenia purpura (ITP), pure red cell aplasia (PRCA), and autoimmune agranulocytosis (AIG).

Immune incompetence is another key feature of CLL, characterized by progressive hypogammaglobulinemia and impaired ability of cell-mediated immunity to recall antigens.\(^2\) Patients with CLL are therefore at increased risk of infections, which are a common cause of morbidity and mortality.\(^1\) In CLL patients, especially those with neutropenia, bacteremia and pneumonia are commonly seen.

The addition of rituximab to fludarabine and cyclophosphamide (FCR) has dramatically improved remission duration and survival of patients with CLL, as evidenced in the landmark CLL-8 study by Hallek, et al. (2010).\(^4\) However, chemotherapeutic regimens such as FCR also increase the risk of cytopenias and opportunistic infections.\(1,4,5\) Effective monitoring and management of cytopenias and infections is therefore of key importance in the treatment of CLL.

Given the impact of CLL and its treatment on the bone marrow and the immune system, it is important to effectively manage hematologic toxicities. Despite the recognition of this concern, strategies to manage these complications vary within and between Canadian institutions. This paper is a general discussion on the management of hematological toxicities in CLL patients treated with FCR. However, it does not reflect a true evidence-based guideline process with a systematic literature review and is not meant to be used as a consensus guideline. The management and prevention of infections through appropriate prophylaxis is beyond the scope of this paper but is an important focus for future discussions.
Selecting patients for treatment with FCR

Patient fitness and comorbidities should be considered in treatment decisions to determine whether aggressive therapies such as FCR can be tolerated. Several systems exist for determining patient fitness, two of the most common being the Eastern Cooperative Oncology Group (ECOG) Performance Status and the Cumulative Illness Rating Scale (CIRS). In determining whether a patient can be categorized as fit, a combination of these scoring systems should be used.6

In 1982, ECOG developed a set of performance status criteria that categorizes patients into one of five categories from high to low levels of physical function. (Table 1) These categories were designed to assess how the patient’s disease affects daily living.7 The ECOG Performance Status categories are also commonly used within the context of CLL to assess treatment intensity and determine whether elderly patients could be included in specific clinical trials.7

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Adapted from Oken, et al 1982
ECOG = Eastern Cooperative Oncology Group

Once a fitness score has been determined based on a combination of the systems discussed, it is possible to group patients into a fit or frail group. (Table 2)

<table>
<thead>
<tr>
<th>Table 2. Patient fitness types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
</tr>
</tbody>
</table>
| Fit group | - ECOG Performance Status 0–2  
- CIRS ≤6 |
| Frail group | - ECOG Performance Status 3–4  
- CIRS >6 |

CIRS = Cumulative Illness Rating Scale;  
ECOG = Eastern Cooperative Oncology Group

By using the methods described above to determine patient fitness, treatment decisions can be made that balance efficacy and individual patient tolerability. If patients are determined to be fit according to the above criteria, FCR is a reasonable first-line treatment option. However, if patients are identified as frail, alternative, less toxic treatment regimens should be used. Less aggressive treatment options that can be considered in frail patients include fludarabine; chlorambucil; or cyclophosphamide, vincristine, and prednisone (CVP); with or without rituximab. For patients with a CIRS score ≥6 and/or ECOG >2 but with renal dysfunction, FCR may still be appropriate in some patients (e.g., CrCl 50–70 mL/min). Fludarabine with rituximab (FR) can be considered with a reduced dose of fludarabine for patients with poor renal function. In addition, for patients falling in between the fit and frail categories, or for those requiring a less aggressive regimen, FR is also a reasonable option. By using these selection methods to eliminate frail patients, hematological toxicities may be minimized or even eliminated completely with the use of FCR.

Managing cytopenias

In determining the appropriate strategy for managing CLL patients with hematological toxicities, it is important to determine whether these are related to the disease itself or to treatment with chemotherapeutic regimens such as FCR. Prior to treatment, bone marrow suppression as a result of CLL itself can lower blood counts due to overcrowding with abnormal lymphocytes. Thus, it is important to treat the disease to restore blood counts. As treatment with FCR also causes myelosuppression, low counts seen with later treatments (cycles 4–6) may occur as a result of chemotherapy itself. At later points in the disease, delaying treatment is therefore appropriate to ensure bone marrow recovery and prevent further toxicity.

Since patients with CLL have low blood counts to begin with, standard criteria for grading hematologic toxicities cannot be applied.4 Therefore, to adequately monitor blood counts and manage cytopenias effectively, it is important to assess baseline counts prior to treatment to establish a basis for comparison.
Once treatment is initiated, periodic blood counts should be documented and compared to baseline levels rather than to normal lab values in order to assess progress. A grading scale of hematologic toxicities for use in CLL was developed by the International Workshop for CLL (IWCLL) and is presented in Table 3. For lower risk patients, blood counts should be monitored 1–2 times per cycle, with more extensive monitoring in earlier cycles. In higher risk patients, such as those with low platelet levels at baseline, weekly blood counts are recommended.10-14 (Figure 1)

### Table 3. Grading of hematologic toxicities in CLL

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Decrease in platelets1 or Hb1</th>
<th>Absolute Neutrophil Count2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change to 10%</td>
<td>≥2.0 × 10^9/L (2000/mm³)</td>
</tr>
<tr>
<td>1</td>
<td>11%–24%</td>
<td>1.5–2.0 × 10^9/L (1,500–2,000/mm³)</td>
</tr>
<tr>
<td>2</td>
<td>25%–49%</td>
<td>≥1.0–1.5 × 10^9/L (1,000–1,500/mm³)</td>
</tr>
<tr>
<td>3</td>
<td>50%–74%</td>
<td>≥0.5–1.0 × 10^9/L (500 and 1,000/mm³)</td>
</tr>
<tr>
<td>4</td>
<td>≥75%</td>
<td>&lt;0.5 × 10^9/L (&lt;500/mm³)</td>
</tr>
</tbody>
</table>

Adapted from Hallek, et al. 2008

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pre-treatment will be recorded as grade 5.

1Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is <2.0 × 10^9/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (i.e. 20 × 10^9/L [20 000/μL]) was present pre-treatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

1Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoetin is irrelevant for the grading of toxicity but should be documented.

1If the absolute neutrophil count (ANC) reaches <1.0 × 10^9/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1.0 × 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

Managing neutropenia

Neutropenia is the most common hematologic toxicity seen in patients with cancer.10 The administration of cytotoxic chemotherapies, such as cyclophosphamide and fludarabine, generally results in a white blood cell nadir after 5–14 days, with recovery by days 7–21. However, high-dose chemotherapy can extend the duration and deepen the nadir of the neutropenia, increasing the risk of infection. Careful monitoring of absolute neutrophil counts (ANC) and comparison to baseline levels is therefore important to ensure neutropenia is managed appropriately.

Although cytopenias associated with cyclophosphamide are well known, treatment with fludarabine can lead to additional myelosuppression.15 Myelosuppression with fludarabine generally has a time to nadir of 10–14 days, with recovery between 5–7 weeks.16 A phase I study in solid tumour patients showed that the median time to nadir counts after treatment with fludarabine was 13 days (range: 3–25 days) for granulocytes and 16 days (range: 2–32 days) for platelets.1 Although most patients had hematologic impairment at baseline either as a result of their disease or prior therapy, use of fludarabine may cause cumulative myelosuppression. Since patients are already immuno-compromised, administration of fludarabine and cyclophosphamide (FC) requires careful hematologic monitoring.

Recombinant granulocyte colony-stimulating factor (rG-CSF) is a supportive care agent that stimulates neutrophil proliferation, differentiation, and activation.10 The 2006 American Society of Clinical Oncology (ASCO) guidelines on the use of white blood cell growth factors recommends the use of G-CSF when the anticipated frequency of febrile neutropenia exceeds 20% or in patients considered at high-risk because of comorbidities (e.g., extensive prior chemotherapy or pelvic radiotherapy, neutropenia existent prior to chemotherapy, or active infection).17 In addition, the protocol for the CLL-8 study mandated the use of G-CSF in the event of neutropenia with fever >38.5 °C or hypothermia with or without suspected or documented infection.4 In the CLL-8 study, 45% of patients treated with FCR and 23% of patients treated with FC received G-CSF during the course of their disease.

Use of growth factors may be useful in certain patients with infection or disease-related bone marrow suppression. However, when neutrophil counts are reduced after cytotoxic therapy, administering growth factors may elevate ANCs, giving physicians a false sense of security that continuing treatment can be done safely. When treatment is resumed prematurely, complete recovery may not have occurred, causing further damage to bone marrow. Further bone marrow damage can impede the ability to give subsequent treatments, resulting in a poorer prognosis for these patients. Therefore, when neutrophil counts are reduced as a result of treatment, FCR should be delayed to allow for adequate recovery before resuming therapy. (Figure 1) Determining the cause of neutropenia is necessary to determine the correct course of action. Generally, when neutropenia occurs early in the disease course, such as between cycles 1 and 3, growth factors may be considered while waiting for bone marrow clearance. Beyond early disease, growth factors should only be used to prevent recurring infections when neutropenia is accompanied by fever.
Before treatment with FCR
Establish baseline blood counts and monitor 1–2 times per cycle in lower risk and weekly in higher risk patients

**Neutropenia**
- Grade 3/4:
  - ANC <1.0x10^9/L

**Thrombocytopenia**
- Grade 3/4:
  - ≥50% decrease in platelet count

**Anemia**
- Grade 3/4:
  - ≥50% decrease in Hb

**Cycle 1–3 Grade 3/4**
Consider using growth factors while waiting for marrow clearance due to disease

1st Grade 3/4 event
- Delay FCR for up to 2 weeks
- Once counts ≥ baseline, consider starting subsequent cycles of FCR with 25% dose reductions of F and C

2nd Grade 3/4 event
- Delay FCR for up to 2 weeks
- Once counts ≥ baseline, start subsequent cycles of FCR with further dose reductions of F and C

3rd Grade 3/4 event
- Delay FCR for up to 2 weeks
- Once counts ≥ baseline, start subsequent cycles of FCR with further dose reductions of F and C
- If counts remain low, FCR should be discontinued

At any point during treatment
Consider platelet transfusion when counts <20,000/µL

At any point during treatment
- If Hb does not rise more than 100 g/L by 8 weeks consider ESAs
- Epoetin or darbepoetin recommended when Hb <100 g/L after treatment
- Hb can be increased to the lowest concentration needed to avoid transfusions
- Hb should not exceed 120 g/L during ESA therapy
- Iron supplementation should be given to augment response to ESAs
- Transfusions of RBCs recommended only for severe anemia with cardiac complications


ANC = absolute neutrophil count; C = cyclophosphamide; ESA = erythropoiesis stimulating agent; F = fludarabine; FCR = fludarabine, cyclophosphamide, rituximab; G-CSF = granulocyte colony-stimulating factor; Hb = hemoglobin
Appropriate upfront selection of patients for treatment with FCR should dramatically reduce the risk of cytopenias in patients with CLL. Therefore, eliminating cyclophosphamide completely to increase neutrophil counts is not recommended. To manage patients with severe neutropenia, treatment delays and dose reductions are appropriate to allow for marrow recovery. In the CLL-8 study, treatment with FCR was delayed and the dose of fludarabine and cyclophosphamide was reduced in patients with grade 3/4 neutropenia. Therefore, when the first grade 3/4 cytopenia is reported, FCR treatment should be delayed for up to two weeks until counts reach or exceed baseline levels. Once counts have recovered, treatment with FCR may be resumed, but the dose of fludarabine and cyclophosphamide should be reduced by 25%. If grade 3/4 neutropenia continues to occur, fludarabine and cyclophosphamide should continue to be reduced. If, however, severe neutropenia occurs for three or more cycles, treatment with FCR should be discontinued and less marrow suppressive rituximab combinations, such as FR or cyclophosphamide, rituximab, dexamethasone (RCD), may be considered if the patient can tolerate them and they have active disease. (Figure 1)

Managing thrombocytopenia

Before beginning treatment with FCR, patients may have thrombocytopenia as a result of marrow replacement by their leukemia; the majority have high-risk disease with platelet levels <100,000/μL. As with neutropenia, thrombocytopenia may also occur as a result of treatment with FCR. When severe thrombocytopenia (grades 3/4) occurs after treatment with FCR, treatment delays and dose reductions of fludarabine and cyclophosphamide should be implemented as per the recommendations above for neutropenia. (Table 4 and Figure 1)

Treatment for thrombocytopenia typically involves platelet transfusions, which are commonly given when platelet levels fall below 20,000/μL. Common risks associated with platelet transfusions include infection, allergic reactions, transfusion-associated lung injury, and alloimmunization. In addition, refactoriness to platelet transfusion can occur due to the development of antibodies. The development of antibodies can become a significant problem for patients who become dependent upon transfusions, although leukocyte filtration can decrease the incidence of this complication.

Managing anemia

Anemia is a common consequence of cancer and its treatment, occurring in approximately 40% of patients. Potential causes of cancer-associated anemia may include direct tumor infiltration of bone marrow; reduced levels of endogenous erythropoietin production; an increase in inflammatory cytokines, such as tumour necrosis factor (TNF) that may directly inhibit erythropoiesis by curbing stored iron utilization; and other contributory factors, such as nutritional deficiencies, hemorrhage, and hemolysis.

The primary treatments for cancer-induced anemia include blood transfusions, erythropoiesis stimulating agents (ESA), such as epoetin alfa; darbepoetin alfa; and iron therapy. Decisions regarding treatment must be tailored to each patient based on the degree of anemia, clinical status, and comorbidities. For patients with severe anemia with continued symptoms such as poor cardiac or respiratory function manifesting as dyspnea, cardiac failure, or angina, treatment should include transfusion of packed red blood cells (RBCs). However, for mild to moderate anemia, blood transfusions are not recommended due to the increased risk of infection, allergic responses, transfusion-associated lung injury, and alloimmunization.

<table>
<thead>
<tr>
<th>Table 4. CLL-8 protocol for cytopenia-related dose reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td>1st Grade 3/4 cytopenia</td>
</tr>
<tr>
<td>2nd Grade 3/4 cytopenia</td>
</tr>
<tr>
<td>3rd Grade 3/4 cytopenia</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Adapted from Hallek, et al. 2010
The 2010 ASCO/ASH guidelines on treating cancer-induced anemia recommend that iron stores be checked at baseline and periodically to optimize symptom improvement.\textsuperscript{11,12} (Table 3 and Figure 1) The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin (Hb) concentration that has decreased to <100 g/L in order to decrease RBC transfusions. Transfusions are also an option, depending on the severity of the anemia or clinical circumstances. An optimal level at which to initiate ESA therapy in patients with anemia whose Hb is between 100–120 g/L cannot be definitively determined from the available evidence. Under these circumstances, the decision to initiate ESA treatment should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences. Hb can be increased to the lowest concentration needed to avoid transfusions, which may vary by patient and condition. However, the Hb concentration should not exceed 120 g/L during ESA therapy.\textsuperscript{14} The guidelines also state that epoetin or darbepoetin are equally effective when treatment calls for ESAs. Regardless of the supportive drug chosen, iron supplementation is advised to augment the response to ESAs.

Autoimmune complications of CLL

Autoimmune complications occur in around 10–25\% of patients with CLL at some point during their disease.\textsuperscript{2,3,16} Blood constituents are the main target, resulting in a number of disorders, including AIHA, ITP, PRCA, and AIG. Of these phenomena, AIHA is the most common.

Patients with CLL receiving FCR should be evaluated and closely monitored for signs of autoimmune cytopenias, which occur in around 6.5\% of treated patients and may be confused with cytopenias related to marrow suppression.\textsuperscript{19} Typically, immune cytopenias should be suspected in patients when there is an isolated fall or delayed recovery in Hb, platelets, or neutrophils.

The development of AIHA following FCR is typically associated with a negative Coomb’s test. The diagnosis of PRCA or ITP usually requires a marrow confirmation.\textsuperscript{4} These conditions usually respond to prednisone with discontinuation of FCR. Patients not responding to prednisone, or relapsing following tapering of the steroid, usually respond to cyclosporine or to combination treatment with RCD.\textsuperscript{20}

Conclusions

CLL is a B-cell malignancy that is distinct from other leukemic diseases and B-cell tumours, with important consequences for its management. The disease itself leads to a number of cytopenias due to overcrowding of bone marrow with abnormal lymphocytes. Although treatment with FCR has improved overall and progression-free survival, cytotoxic regimens such as these can worsen cytopenias through treatment-related myelosuppression.

Upright selection of fit patients who are better able to tolerate more aggressive regimens such as FCR can effectively reduce the risk of cytopenias. Further, by using a combination of tools such as the ECOG and CIRS to categorize patients, treatment decisions can be made based on fitness level to ensure therapy is well tolerated.

Given the distinct nature of CLL from other diseases, standard criteria for grading the severity of cytopenias are not appropriate. It is therefore important to monitor blood counts before and during treatment to effectively manage toxicities. When cytopenias occur as a result of the disease itself, treatment with chemotherapy is important to reduce lymphocyte burden. However, when hematologic toxicities occur as a result of treatment, dose delays and reductions may be necessary to allow adequate recovery of bone marrow. Given the impact of hematological toxicities on adherence to treatment, effective management is crucial to ensure optimal treatment response and remission.

APPENDIX A: Calculating the fourteen-system modified Cumulative Index Rating Scale (CIRS)

Patient name: ___________________________  Diagnosis: ___________________________
Date: _______________  Medical details: ___________________________
Doctor: ___________________________  Hospital ID number / HC #: ___________________________

<table>
<thead>
<tr>
<th>Scale¹,²</th>
<th>Rating malignancies¹</th>
<th>Fourteen-system modified version of CIRS¹,³</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – No problem affecting that system</td>
<td>Rated 0</td>
<td>SYSTEM</td>
</tr>
<tr>
<td>1 – Current mild problem or past significant problem</td>
<td>Rated 1</td>
<td>Cardiac</td>
</tr>
<tr>
<td>2 – Moderate disability or morbidity and/or requires first-line therapy</td>
<td>Rated 2</td>
<td>Vascular</td>
</tr>
<tr>
<td>3 – Severe problem and/or constant and significant disability and/or hard-to-control chronic problems</td>
<td>Rated 3</td>
<td>Hematological</td>
</tr>
<tr>
<td>4 – Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment</td>
<td>Rated 4</td>
<td>Respiratory</td>
</tr>
</tbody>
</table>

Ratings¹
- No problems or healed minor injuries
- Past childhood injuries
- Minor surgery (e.g., amygdalectomy)
- Uncomplicated healed fractures
- Other past problems healed without sequel

Rated 1
- Current medical problem with mild discomfort or disability, or occasional exacerbations
- Minor impact on morbidity
- Past significant medical problems not currently an issue
- Major surgery (e.g., hysterectomy)

Rated 2
- Medical condition that requires daily treatment (first-line therapy) (e.g., steroids – asthma, H₂ blockers – acid reflux)
- Moderate disability or morbidity

Rated malignancies¹
- Cancer diagnosis without evidence of recurrence in past 10 years, and skin cancer sporadic in past without recurrence or sequel (other than melanoma)

Rated 1
- No evidence of recurrence or sequel in past 5 years

Rated 2
- Recurrent malignancy or metastasis (other than lymph) or palliative treatment stage

Fourteen-system modified version of CIRS¹,³

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>RATING/SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>- Any cardiac problems (e.g., angina, myocardial infarction, arrhythmia, valve problems)</td>
<td></td>
</tr>
<tr>
<td>- Any medication taken for above</td>
<td></td>
</tr>
<tr>
<td>- Heart surgery in past</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>- Circulation problems (e.g., peripheral arterial disease, aneurysm, abdominal aorta), or hypertension, dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>- Any medication taken for above</td>
<td></td>
</tr>
<tr>
<td>- Vascular surgery in past (e.g., bypass, grafts of lower limbs, carotid endarterectomy)</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>- Blood problems (e.g., anemia, leukemia, coagulation issues, thrombosis, embolism)</td>
<td></td>
</tr>
<tr>
<td>- Blood cells, spleen, lymphatic problems</td>
<td></td>
</tr>
<tr>
<td>- Any medications taken for above</td>
<td></td>
</tr>
<tr>
<td>- Note: patients taking anticoagulants belong to this system if the main problem is of hypercoagulability (thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in “Cardiac”.</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>- Any respiratory problems (asthma, emphysema, bronchitis, pulmonary embolism)</td>
<td></td>
</tr>
<tr>
<td>- Any medications taken for above</td>
<td></td>
</tr>
<tr>
<td>- Lung surgery</td>
<td></td>
</tr>
<tr>
<td>- Cigarette smoking (pack years = # packs per day x # years smoked)</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal: 

Smoking: Rated 1 – Up to 20 pack years
Rated 2 – 21-40 pack years
Rated 3 – over 40 pack years
Patient name: ______________________  
Date: ______________________

Ophthalmological/otorhinolaryngology  
- Any problems with eyes (glaucoma, cataract, loss of vision), ears, nose, throat or voice issues (loss of hearing, vertigo/dizziness unless neurological)  
- Any medications taken for above  

Upper gastrointestinal  
- Any problem with stomach and/or digestion (esophagus, duodenum)  
- Any medications taken for above  
- Surgery for stomach or esophagus

Lower gastrointestinal  
- Any intestinal problems (intestinal hernia, constipation, incontinence or anal problems)  
- Any medications taken for above  
- Abdominal surgery

Hepatic/pancreatic  
- Any liver or pancreas problems  
- Any medications taken for above  
- Surgery for liver or pancreas (cholecystectomy rated here)

Renal  
- Any kidney problems (impairment in function, infections)  
- Any medications taken for above  
- Surgery for kidneys

Genitourinary  
- Any urinary problems ( lithiasis, incontinence)  
- Any medications taken for above  
- Surgery for bladder or renal lithiasis

Musculoskeletal & tegumental  
- Any problems in the skin, joints, bones, muscles (arthritis, osteoporosis, carpal tunnel, fibromyalgia and any other skin/musculoskeletal problem)  
- Any medications taken for above (anti-inflammatory, infiltrations, creams)

Neurological  
- Any neurology problems (cerebrovascular disease, accidents, peripheral neuropathy, headaches)  
- Any medications taken for above  
- Surgery for these problems

Endocrine, metabolic, breast  
- Any problems of thyroid, obesity, diabetes, or hormonal problems  
- Obesity ................................................................. Rated 1 - BMI ≥ 30  
- Any medication or surgery for any of these problems .......................................................... Rated 2 - BMI ≥ 30 + meds or moderate disability  
- Any problems with breasts (dysplasia, cancer)  
- Any problems with breast (dysplasia, cancer) .......................................................... Rated 3 - BMI ≥ 45  
- Surgery for these problems  
- Menopause/andropause, any hormone .......................................................... Rated 0 - without hormonotherapy or symptoms  
- Menopause/andropause, any hormone .......................................................... Rated 1 - symptomatic or with hormonotherapy

Psychiatric  
- Any problems of depression, anxiety, alcohol or drug abuse, or other problems  
- Personality problems/disorders  
- Any medications taken for above

**TOTAL SCORE**  
- Only one score is given for each system  
- Total score = sum of all scores

Adapted from Linn BS, et al, and Hudon C, et al.1,2

References:  

© Copyright 2011, Hoffmann-La Roche Limited
New Evidence in Oncology is an independent medical news reporting service providing educational updates on current medical events. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsors. Support for the development and distribution of this report was provided by Hoffmann-La Roche Hematology, Lundbeck Oncology, and Pfizer Oncology. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information. No claims or endorsements are made for any products, uses, or doses presently under investigation. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate understanding of current trends in oncology for physicians and allied healthcare providers.