

## **ACUTE MYELOID LEUKEMIA**

Date Developed: May, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Lymphoma/Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## **Background**

Acute myeloid leukemia (AML) is a group of infrequent neoplasms responsible for a significant number of cancer-related deaths. Its incidence has been relatively stable over the last years at about 3.7 per 100 000 persons per year in the western world. It is primarily a disease of later adulthood with an increasing incidence with age. The median age at diagnosis is 65 years with a slight male preponderance. Outcome varies greatly according to age at diagnosis due to disease and patient features. Untreated AML is a uniformly fatal disease with a median survival of 11-20 weeks.<sup>1</sup>

The etiology of AML in most cases is unclear. Known risk factors include exposure to chemotherapeutic agents particularly alkylating agents, topoisomerase-II inhibitors and taxanes as well as both therapeutic and nontherapeutic radiation. A higher than average incidence is seen in individuals with Down's syndrome, Klinefelter's syndrome, Ataxia telangiectasia, Kostman syndrome, neurofibromatosis or Fanconi anemia. Exposure to benzenes, pesticides, herbicides and cigarette smoking may also play a role in its development. There is also a greater incidence of AML in individuals with pre-existing hematologic disorders such as the myelodysplastic syndromes or myeloproliferative disorders.

## **Guideline Goals/ Objectives**

- Delineate the diagnostic criteria for acute myeloid leukemias
- Delineate the prognostic markers in acute myeloid leukemias
- Identify the management options for acute myeloid leukemias in adults including chemotherapy, hematopoietic stem cell transplantation, and palliation

## **Guideline Question**

What is the optimal management of the acute myeloid leukemias in Alberta at the present time?

## **Development Panel**

This guideline was developed by the Alberta Provincial Lymphoma/ Hematology Tumour Team. The team is comprised of surgical oncologists, radiation oncologists, pathologists, pharmacists, nurses, and medical oncologists.

## **Search Strategy**

The MEDLINE (1996 through October 2008), ASCO abstracts and proceedings, and ASH abstracts and proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials.

## **Discussion**

### **Diagnosis**

AML describes a heterogeneous group of clonal hematopoietic progenitor cell disorders with a spectrum of morphologic, immunophenotypic, cytogenetic and molecular characteristics.

**Diagnostic Tests:** The diagnosis is often suspected and can at times be confirmed from the peripheral blood. However, all patients being considered for therapy should undergo a bone marrow aspiration and biopsy. Samples should be sent for morphology, flow cytometry, cytogenetics and molecular analysis. Immunophenotyping by flow cytometry confirms myeloid lineage and stage of differentiation of the malignant cell. It may have a prognostic role by establishing a unique phenotype for minimal residual disease monitoring. A full karyotype will be determined at diagnosis in all cases. Fluorescence in-situ hybridization (FISH) will also be carried out in cases morphologically suspicious for specific subsets. Molecular analysis will be carried out in cases suspicious for promyelocytic leukemia, core binding factor leukemias as well as cases with normal karyotypes looking for the PML/RAR $\alpha$  fusion gene, abnormalities of c-Kit and FLT3 respectively<sup>2</sup>.

**Diagnostic Criteria:** The threshold number of immature clonal cells, typically blasts, required to make the diagnosis of AML is 20% of non-erythroid cells in the bone marrow. Exceptions include AML with t(8;21), inv(16) or t(15;17), in which the diagnosis of AML is made regardless of the percentage of bone marrow blasts<sup>3</sup>. De novo AML should refer to patients with no clinical history of prior myelodysplastic syndrome, myeloproliferative disorder or exposure to potentially leukemogenic therapies or agents. Secondary AML should refer to patients with prior hematologic disease.

## **Classification**

The blast count, lineage commitment, and level of differentiation of the neoplastic cells have long been the basis of AML classification. The WHO classification includes features such as genetic abnormalities at the chromosomal and/or molecular level and history of previous therapy or antecedent hematologic disease. The AML portion of the WHO classification of myeloid neoplasms is therefore<sup>3</sup>:

### Acute Myeloid Leukemias

- AMLs with recurrent cytogenetic translocations

  - AML with t(8;21)(q22;q22), AML1 (CBF-alpha)/ETO

  - Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR alpha)

  - AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or

  - t(16;16)(p13;q11), CBF $\beta$ /MYH11X)

  - AML with 11q23 (MLL) abnormalities

- AML with multilineage dysplasia

  - With prior myelodysplastic syndrome

  - Without prior myelodysplastic syndrome

- AML, therapy related

  - Alkylating agent-related

  - Epipodophyllotoxin-related

  - Other types

- AML not otherwise categorized

  - AML minimally differentiated

  - AML without differentiation

  - AML with maturation

  - Acute myelomonocytic leukemia

  - Acute monocytic leukemia

  - Acute erythroid leukemia

  - Acute megakaryocytic leukemia

  - Acute basophilic leukemia

Acute panmyelosis with myelofibrosis  
Acute biphenotypic leukemia

### Ancillary Tests

Other bloodwork to be done at diagnosis includes: INR, PTT, fibrinogen, electrolytes, calcium, magnesium, phosphatase, creatinine, ALT, alkaline phosphatase, total and direct bilirubin and uric acid. Viral serologies should be drawn including HSV, VZV, CMV as well as hepatitis B and C. Testing for syphilis should also be done with the VDRL screen. A chest X-ray should be performed at diagnosis as a baseline. Cardiac function should be assessed by means of an echocardiogram or nuclear medicine cardiac scan. A lumbar puncture should be done if there are otherwise unexplained neurological symptoms and appropriate imaging rules out a mass lesion. A screening lumbar puncture should be done in cases of myelomonocytic or monocytic AML or in those with a presenting blast count of greater than  $100 \times 10^9/L$  as soon as circulating blasts have been cleared and the platelet count is greater than 50 (transfused or unsupported).

Human leukocyte antigen typing of the patient and all available siblings should be performed at the time of diagnosis if the patient would be eligible for hematopoietic stem cell transplantation.

### Response Criteria<sup>2</sup>

- Morphological leukemia-free state – less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells
- Morphological complete remission (CR) – morphological leukemia free-state and an absolute neutrophil count of more than  $1.0 \times 10^9/L$  and platelets of at least  $100 \times 10^9/L$
- Cytogenetic complete remission – this category is recommended primarily for use in clinical research studies but likely to be informative
- Molecular complete remission – recognized as a therapeutic objective in acute promyelocytic leukemia but still controversial in other subsets
- Treatment failure – treatment has failed to achieve a CR, can be due to resistant disease or death
- Relapse – a reappearance of leukemic blasts in the peripheral blood or greater than 5% blasts in the bone marrow not attributable to any other cause

### Prognosis

Several factors influence the ability to achieve and maintain a complete remission in acute myeloid leukemia. The most important of these are **age** and **cytogenetic abnormalities**. **Molecular findings** are also emerging as having probable important significance. AML evolving from a myelodysplastic disorder or myeloproliferative disorder is often more resistant to cytotoxic chemotherapy than de novo AML. However, it may also have a more indolent course. A white count greater than  $100 \times 10^9/L$  at diagnosis may also confer a higher risk of relapse, as does the need for greater than one cycle of induction chemotherapy to achieve a complete remission.

**Age:** Older patients have a higher prevalence of unfavorable cytogenetics and antecedent myelodysplastic/myeloproliferative disorders, higher incidence of multidrug resistance and an increased frequency of comorbid medical conditions that affect the ability to tolerate intensive treatment<sup>4</sup>. Even when standard chemotherapy is given outcomes are generally inferior to those

achieved in younger patients<sup>5</sup>. Treatment related mortality often exceeds any expected transient response in this group.

**Cytogenetics:** Karyotype represents the single most important prognostic factor for predicting remission rate, relapse, and overall survival. Three groups of cytogenetic abnormalities have been defined with respects to these outcomes classified as favorable, intermediate and unfavorable risk. For example, in a retrospective review of 1213 AML patients treated on CALGB protocols up to the year 2000, the 5-year survival rate was 55% for patients with favorable cytogenetics, 24% for patients with intermediate cytogenetics and 5% for those with poor risk cytogenetics<sup>6</sup>. This categorization holds whether the therapy includes stem cell transplantation or consolidation with chemotherapy alone<sup>6-11</sup>. See table 1 for the cytogenetic classification. Cytogenetics at diagnosis retain their independent predictive value in the older AML patient population<sup>12, 13</sup>.

Table 1. Cytogenetic classification.

Classification	SWOG Criteria	MRC criteria: As for SWOG, except:
Favorable	t(15;17) – with any other abnormality inv(16)/t(16;16)/del(16q) – with any other abnormality t(8;21) – without del(9q) or complex karyotype	t(8;21) – with any other abnormality
Intermediate	+8, -Y, +6, del(12p) normal karyotype	abn 11q23 del(9q), del(7q) – without other abnormalities Complex karyotypes (≥ 3 abnormalities, but <5) All abnormalities of unknown prognostic significance
Unfavorable	-5/del(5q), -7/del(7q) t(8;21) with del(9q) or complex karyotype inv(3q), abn 11 q23, 20q, 21q, del(9q), t(6;9) t(9;22), abn 17p Complex karyotypes (≥ 3 abnormalities)	Complex karyotypes (≥ 5 abnormalities)
Unknown	All other clonal chromosomal aberrations with fewer than 3 abnormalities	

Abbreviations: SWOG – Southwestern Oncology Group, MRC – Medical Research Council, abn - abnormalities

**Molecular abnormalities:** In addition to basic cytogenetic analysis, new molecular markers are helping refine prognostic groups. These include FMS-like tyrosine kinase 3 (FLT3), c-Kit and nucleophosmin 1 (NPM1). Several recent large series have demonstrated worse relapse-free survival with partial tandem duplication of FLT3, particularly in patients with a normal karyotype<sup>14-19</sup>. An isolated NPM1 mutation confers an improved survival to patients with normal karyotype similar to patients with favorable cytogenetics<sup>20-25</sup>. Patients who have combined NPM1 and FLT3 mutations have intermediate risk<sup>21-24, 26</sup>. In patients with favorable karyotypes, t(8;21) or inv 16, the presence of a mutation in c-Kit significantly increases the risk of relapse<sup>27-29</sup>.

In patients with acute promyelocytic leukemia, the PML/RAR $\alpha$  mutation also serves as a molecular marker and is present by definition.

## Risk Groups

### **Good Risk Patients:**

- This group is defined by the favorable cytogenetic abnormalities as described above.
- In those patients with t (8;21) or inversion 16 with c-Kit mutations consideration should be given to following the recommendations for intermediate risk patients.

- AML with t(15;17) and its variants is considered have one of the best likelihood of cure with tailored therapy and is discussed separately.

#### ***Intermediate Risk Patients:***

- This group is mainly defined by the cytogenetic abnormalities as describe above.
- In those patients with normal cytogenetics and FLT3 mutations consideration should be given to following the recommendations for high risk patients.

#### ***High Risk Patients:***

- This group includes patients with unfavorable cytogenetics as well as those with secondary or therapy-related AML.
- Also included are those patients with a white blood cell count greater than  $100 \times 10^9/L$  at diagnosis and those who require more than one cycle of induction chemotherapy to achieve a complete remission.
- Patients with acute erythroid and acute megakaryocytic leukemia are generally considered to be in this group of patients.
- All relapsed patients are considered high risk.

#### **Treatment<sup>30-32</sup>**

The initial goal of therapy for AML is to achieve a complete remission, given that a complete remission with currently available therapy is requisite, although not sufficient for a cure. It is the sole outcome currently associated with improved survival. Chemotherapy is the mainstay of treatment. Poor performance status and comorbid medical conditions, in addition to age, are factors which influence the ability of an individual to tolerate induction therapy.

In patients undergoing any therapy beyond supportive care a central venous catheter ideally should be placed.

Supportive care in all patients includes red blood cell transfusions for symptomatic anemia. Platelets should be transfused at a threshold of  $10 \times 10^9/L$  if there is no evidence of bleeding or to keep a platelet level of around  $50 \times 10^9/L$  if there is active bleeding.

Tumor lysis prophylaxis with allopurinol should be initiated in all patients. Monitoring for electrolyte abnormalities and renal function should be ongoing during the first few days of induction chemotherapy particularly in patients with significantly elevated white blood cell count.

Antifungal prophylaxis should be considered during all phases of chemotherapy depending on local incidence of invasive fungal infections<sup>33</sup>. Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guidelines<sup>34</sup>.

The use of growth factor support should be individualized and should be considered in elderly patients after chemotherapy and in those with documented infections or persistent fevers despite appropriate antimicrobial therapy. Recent use of G-CSF can increase the blast count in a bone marrow specimen obtained to determine remission status, however immunophenotyping may be useful in this situation if the leukemic cells are known to have an abnormal phenotype.

Steroid eye drops are recommended during the administration of intermediate to high dose cytarabine to prevent conjunctivitis. These patients should also be screened for cerebellar toxicities before each dose of cytarabine.

Rare patients who present with extramedullary disease should be treated with systemic therapy. Local therapy (surgery/radiotherapy) may be useful for residual disease).

## *Under Age 65*

### *Induction*

Chemotherapy should consist of standard-dose cytarabine with an anthracycline, so called 7&3 chemotherapy ( see appendix A for regimen). Studies looking at higher doses of cytarabine in induction have not shown an increased CR rate but have demonstrated an increased treatment related mortality<sup>35-37</sup>.

At count recovery or about day 30-35 from the start of chemotherapy a bone marrow aspirate should be done to determine remission status. The likelihood of establishing a CR with one cycle of induction chemotherapy varies amongst prognostic groups but overall is in the order of 60-70%. Day 14 bone marrow aspirates are currently controversial but may be informative.

### *Re-induction*

If CR is not achieved after one cycle of induction chemotherapy another attempt is appropriate. This may consist of a repeat of 7&3 chemotherapy or alternatively a different regimen such as NOVE, FLAG-Ida, or high dose cytarabine (HiDAC) (see appendix A for regimens) may be tried.

A bone marrow aspirate and biopsy should be done at count recovery or day 30-35 to document remission status. The likelihood of a second regimen being successful is in the order of 50%. If no remission is achieved after 2 cycles of induction chemotherapy palliation essentially becomes the goal of care.

### *Consolidation*

If CR has been achieved further therapy is necessary for potential cure. The nature of consolidation therapy must be individualized for each patient based on a risk analysis of the risk of relapse of the AML versus the risk of the proposed consolidation therapy. This will depend on prognostic features of the leukemia, response to therapy, performance status and type of hematopoietic stem cell donor available. HiDAC is the mainstay of consolidation chemotherapy as there has been shown to be a dose intensity effect to cytarabine suggesting that HiDAC is necessary in induction or consolidation.<sup>35,38</sup>

Generally at least one cycle is administered in all patients if only to allow for planning of an allogeneic stem cell transplant although the absolute need for this is controversial. Autologous stem cell transplantation shows some superiority in event-free survival over chemotherapy alone for consolidation,<sup>39-44</sup> however is not routinely recommended unless a donor is not available.

- *Good risk patients:* In patients with AML with t(8;21) or inv 16, data suggests that provided there are no additional risk factors multiple cycles of HiDAC provide higher overall survival than lower doses of cytarabine or stem cell transplant.<sup>45-49</sup> Our recommendation is 2-3 cycles of HiDAC post induction chemotherapy.
- *Intermediate risk patients:* HiDAC has been shown to be preferable over lower dose cytarabine in this cytogenetic group as well<sup>45,50</sup> but its superiority over stem cell transplantation has not been established. It is generally recognized that an allogeneic stem cell transplant provides a decreased relapse rate at cost of increase treatment related mortality when compared to consolidation

chemotherapy or autologous transplantation.<sup>39,42,51,52</sup> The transplant related mortality gap between match related and unrelated donors has been shown to be significantly reduced in recent years.<sup>53,54</sup> A suitable hematopoietic stem cell donor should be sought. If a matched sibling donor is found a related myeloblastic stem cell transplant should proceed as soon as possible, ideally after one dose of HiDAC. If there are no suitable family donors, the patient should proceed through 2-3 cycles of HiDAC consolidation while a match unrelated donor is sought. If one is found before the third cycle of consolidation chemotherapy, consider matched unrelated donor stem cell transplantation.

- *High risk patients:* All efforts should be undertaken to find a matched donor, related or unrelated for eligible patients. During that time the patient should receive ongoing cycles of HiDAC chemotherapy up to a total of 3 cycles. The patient should proceed to allogeneic stem cell transplantation as soon as a donor is identified. Consideration should be given to proceeding to an unrelated cord blood transplant if a suitable cord blood unit is available.

#### *Relapse*

- *Re-induction:* An attempt at achieving a CR should be attempted. If the remission was greater than one year 7&3 chemotherapy can be used again. Otherwise other regimens such as FLAG-Ida, NOVE or HiDAC are appropriate.
- *Hematopoietic stem cell transplantation:* If a stem cell transplant was not done in first CR it should be undertaken once a second CR has been achieved. The ideal donor would be an allogeneic matched related or unrelated donor, or if necessary a cord blood unit. If no suitable donor or cord blood unit is found consider an autologous stem cell transplant.

#### *Palliation*

If co-morbid conditions affect the ability to proceed with optimal aggressive therapy palliation with best supportive care should be considered. This is also an appropriate approach in the setting of primary induction failure or relapse, particularly after allogeneic stem cell transplantation.

#### *Over Age 65:*

In patients with a normal karyotype, the remission rate is 40-50% with cytarabine combined with idarubicin, daunorubicin or mitoxatrone. In those with complex cytogenetics the chance of achieving a remission is approximately 25% with an equivalent 30 day mortality<sup>13</sup>. Attempts to modify this by adjusting the chemotherapy regimens, adding growth factors or multidrug resistance protein regulators have not been successful.<sup>55-58</sup> Due to the poor outcomes in this group, clinical trials are particularly important.

#### *Palliation*

In this age group depending on comorbid conditions and biological age best supportive care is appropriate front-line therapy. This may include hydroxyurea or low-dose cytarabine to minimize the effects of an increasing white count.

#### *Induction*

In patients with an ECOG performance status of 2 or less and no prohibitive comorbid conditions, standard 7&3 induction chemotherapy is appropriate.<sup>59</sup> If consideration is being given to consolidation

therapy or re-induction in the case of primary induction failure, a bone marrow aspirate should be performed to document remission. If no further therapy is planned this can be omitted.

### *Consolidation*

Consolidation chemotherapy in this group of patients is controversial. There is evidence to suggest that low-dose, prolonged ambulatory treatment should be preferred to intensive chemotherapy;<sup>61</sup> however intermediate dose cytarabine can be considered if the patient maintains a good performance status, normal renal function, and has a good or normal karyotype. Consolidation has not been shown to prolong survival in patients with high risk karyotypes.

### *Relapse*

In this age group, if acute leukemia recurs palliation with best supportive care is indicated if there are no available clinical trials.

### **Follow Up**

Once all therapy is completed no further bone marrow aspirates are indicated unless there is concern of relapse or loss of graft in transplanted patients. Regular complete blood counts should be performed every month for the first few years then every 3 months until 5 years. The risk of recurrence after 5 years is very low and hematological follow up can be stopped at that point. Patients should be reminded of the signs and symptoms of leukemia including those of anemia, thrombocytopenia and infection and instructed to seek medical attention at any point if these develop. If there is concern of a relapse at any point, a bone marrow aspirate and biopsy should be performed and the patient should be sent for all the appropriate diagnostic tests.

### **Acute Biphenotypic Leukemia**

These should be treated with a protocol containing agents active in both myeloid and lymphoid leukemias such as FLAG-Ida.

### **CNS Prophylaxis/ Disease Treatment**<sup>30</sup>

Leptomeningeal involvement in AML is present in about 3%. In patients with neurological symptoms imaging should be done to rule out a mass or bleed. If neither of these is present a lumbar puncture should be done. If this is negative for leukemic cells initially it should be repeated if the symptoms persist. If it is positive intrathecal chemotherapy should be administered twice a week concurrently with induction chemotherapy until the cerebrospinal fluid is no longer positive. An additional 2 intrathecal treatments should then be administered. Intrathecal chemotherapy should consist of alternating single agent cytarabine and methotrexate or “triple therapy” with cytarabine, methotrexate and hydrocortisone.

In patients with myelomonocytic or monocytic leukemia as well as those with a presenting blast count of greater than  $100 \times 10^9/L$  a screening lumbar puncture should be done at diagnosis with intrathecal chemotherapy administered at the same time. If the cerebrospinal fluid is positive for leukemic cells the patient should be treated as above. If it is negative a total of 5 prophylactic intrathecal therapies should be administered.

## Future Directions

Gemtuzumab ozogamicin is approved for and recommended for use in first relapse in the elderly in the United States<sup>61</sup>. It is only available for this indication in this country by Special Access through Health Canada. It is currently being investigated added to induction chemotherapy in a large multicentre trial in which the Cancer Corridor is participating<sup>62</sup>.

NPM1 molecular testing should be implemented within the year and may alter the recommendations for therapy in patients with a normal karyotype.

Non-myeloablative protocols are being considered to extend the patient eligibility to those patients over the age of 65.

It is our goal to have a clinical trial, investigating new agents or new combinations, applicable to every patient and participation in these is encouraged.

## **Glossary of Abbreviations**

<b>Acronym</b>	<b>Description</b>
ALT	alanine aminotransferase (liver enzyme)
AML	Acute Myeloid Leukemia
CALGB	Cancer and Leukemia Group B
CMV	cytomegalovirus infection
CNS	central nervous system
CR	complete remission
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence in-situ hybridization
FLAG-Ida	fludarabine + cytarabine + G-CSF + idarubicin
FLT3	FMS-like tyrosine kinase 3 (molecular marker)
G-CSF	granulocyte colony stimulating factor
HiDAC	high-dose cytarabine
HSV	herpes simplex virus
IDSA	Infectious Diseases Society of America
INR	international normalized ratio
MRC	Medical Research Council
NOVE	mitoxantrone + etoposide
NPM1	nucleophosmin 1 (molecular marker)
PML	promyelotic leukemia
PTT	partial thromboplastin time
RAR $\alpha$	retinoic acid receptor, alpha
SWOG	Southwest Oncology Group
VDRL	Venereal Disease Research Laboratory test
VZV	varicella zoster virus
WHO	World Health Organization

## Implementation Strategy

- Present the guideline in the tumour group meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Communicate (electronically) web-posting of the guideline with all the stakeholders.

## Evaluation Strategy

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

## Declaration of Conflict of Interest

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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## **Appendix A: Chemotherapeutic Regimens**

### **7&3:**

- Cytarabine 200 mg/m<sup>2</sup>/d continuous infusion days 1-7
- Idarubicin 12 mg/m<sup>2</sup>/d or Daunorubicin 60 mg/m<sup>2</sup>/d days 1-3

### **NOVE:**

- Mitoxantrone 10 mg/m<sup>2</sup>/d days 1-5
- Etoposide 100 mg/m<sup>2</sup>/d days 1-5

### **FLAG-Ida:<sup>63</sup>**

- Fludarabine 30 mg/m<sup>2</sup>/d days 1-5
- Cytarabine 2 g/m<sup>2</sup>/d days 1-5
- Idarubicin 10 mg/m<sup>2</sup>/d days 1-3
- G-CSF 300 µm s/c od starting day 7

### **HiDAC:**

- Cytarabine 3 g/m<sup>2</sup> every 12 hours on days 1, 3 and 5

### **Intermediate Dose Cytarabine:**

- Cytarabine 1 g/m<sup>2</sup> every 12 hours on days 1, 3 and 5

## **Appendix B: ECOG Performance Status<sup>64</sup>**

0. Fully active, able to carry on all pre-disease activities without restriction
1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3. Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.