



RAJIV GANDHI CANCER INSTITUTE & RESEARCH CENTRE

Newsletter

Price : 50 Paise
Issue : Mar. 2012

Vol. XVI

No. 3

SECTOR-V, ROHINI, DELHI-85 • Tel. : 47022222 (30 Lines) 27051011-1015, Fax : 91-11-27051037

EDITORIAL

SECOND OPINION : WHY, WHEN AND WHO?

When diagnosis of cancer is made, there is much fear, misunderstanding and many questions arise about therapy. It is not unreasonable for a patient to want to have another point of view. What we call a second opinion. Patients have doubts about what is the best way to proceed. Information obtained from internet, newspaper, magazines or from friends is often mixed and confusing. Often there are several approaches to a problem and sometimes there is no definitive answer given the limitations of current medical science.

In life we choose between two things e.g. Ford or Maruti; this house or that house; this mobile or that mobile. Either choice is the positive decision but about cancer it is negative. I don't want surgery or I don't want RT or I want to avoid chemotherapy. We are not used to making choices about things we don't want. It feels strange. That is why it is important to talk to health professional preferably an oncologist who can explain the patient about the various options.

Second opinion should not be a threat to patient's 1st doctor. Patient should be a member of team. Patient should say "I am pleased with your care but I want to have additional input from someone with different perspective". In fact patient's primary physician should welcome the opportunity to have another consultant review and approve his care decision or perhaps suggest a new, clever novel idea that might be to patient's benefit. Yes, there are instances when there is disagreement about treatment. Sometimes patients need to change doctors. But that is not the usual reason for second opinion. Most of the time patients simply want to be sure that there is no stone left unturned in his care.

Second opinion may help in:

- 1) Deciding for patient which choice makes most sense.
- 2) Reassuring patient that his own doctor has made the best choice for him.
- 3) Outlining some of the future choices that need to be made later.
- 4) Defining a new treatment or pathway that may not be generally known (trial setting).

Second opinion consultant should be respectful of the hard work and dedication of the principal doctor and careful to be entirely professional and give credit and validity to those decisions already made. After all their patients have also obtained second opinion, too!!

If patient comes to me for second opinion. There are some golden rules which I follow:-

- Rule I** - I clarify that they will continue their care with their primary oncologist.
- Rule II** - If there is uncertainty about diagnosis and treatment. I recommend another person within my institution who would offer most useful consultation. I may discuss the case in institutional Tumour Board or MSC (Multi Specialty Clinic).
- Rule III** - If at any time they wish to have even 3rd opinion. I would be happy to provide records, test results, x-rays and pathology reports to whomsoever they wish. If they would like me to select and help arrange a third opinion, I would be available to do so.

When to get 2nd opinion?

There is no cook book which tells the patients when to have second opinion. Here is a list of some reasons which guide the patient when to take second opinion:

- 1) If patient has not been given any hope, there is nothing to lose by getting a second opinion. There is a small chance of some error of judgement; a second opinion could save patients life. Sometimes tumours deemed inoperable by one surgeon are found to be operable by another.
- 2) If tumour is of borderline operability patient may be given preoperative CT or RT to make it resectable. Chance of resectability may increase with Preop. CT/RT.
- 3) If patient wants to be in clinical trial, think of a second opinion before signing up or giving consent or you may ask your GP to discuss with the treating doctor. Rules of the trial are generally fixed by team of experts and not treating doctor. An objective second opinion is in order!
- 4) If it is a rare cancer, patient may have second opinion in same hospital or same city and even in other country through tele consultation.
- 5) If it is cancer of unknown origin and make sense to have second opinion to make sure that all appropriate tests have been done. Patient should also consider pathology second opinion in this situation.
- 6) Pathology Second Opinion - Entire treatment plan depends on interpretation of biopsy or surgical specimen. If pathology report does not give definite diagnosis and speaks of only differential diagnosis, a second opinion is probably in order. If pathology report does not correlate with clinical profile, treating doctor himself should insist on second opinion.

Who should give 2nd opinion?

- 1) A Research hospital or major cancer centre is usually a good place to get a second opinion. Since they should be up on the latest in treatment and diagnosis.
- 2) Tumour Boards - Most cancer hospitals have tumor boards where group of experts meet and consider the best treatment option. If your doctor doesn't seem to have a clear recommendation for you, consider asking if he could present patient's case in tumour board.
- 3) Opinion from different specialist - Breast cancer is treated by Surgeons, Cancer Surgeons, Radiotherapist and Medical Oncologists. Surgeons may say that patient does not need further treatment but it is worth taking an opinion from other specialist for any adjuvant treatment. In good cancer centre, usually surgeons refer the patient to experts of other specialties or cases are discussed in Tumour Boards.
- 4) Super specialty Experts - Rarely special treatment like biologic therapy for melanomas, gamma knife for small inaccessible brain tumour is required and your treating doctors know about such superspecialists who are doing special tasks.

Remember an Oncologist is patient's partner in the pathway towards success.

Welcome and encourage second opinion!!

Dr. Dewan A K
Medical Director

ACUTE MYELOID LEUKEMIA – An Update

Acute myeloid leukemia (AML) is not a single disease but a heterogeneous group of neoplastic disorders characterized by the proliferation and accumulation of immature hematopoietic cells in the bone marrow and blood. These malignant cells gradually replace and inhibit the growth and maturation of normal erythroid, myeloid, and megakaryocytic precursors. AML represent approximately 1.2% of all cancer deaths in the United States. 13,780 new cases and 10,200 deaths from acute myeloid leukemia (AML) are estimated in the United States in 2012.

CLINICAL MANIFESTATIONS

The presenting signs and symptoms of AML are nonspecific and are related to decreased production of normal hematopoietic cells and invasion of other organs by the leukemic cells. Patients usually complain of a brief viral-like illness characterized by fatigue and malaise or may present with a progressive skin infection after a minor abrasion. Diffuse bone tenderness involving the long bones, ribs, and sternum is the initial clinical manifestation in 25% of patients. Myeloid granulocytic sarcomas (chloromas) are collections of blasts in extramedullary sites, which may present as isolated subcutaneous masses and may be confused with a primary or metastatic carcinoma.

Diagnosis

In many cases diagnosis is possible based on examination of the peripheral blood smear. However, a bone marrow aspirate should be performed to confirm the leukemia subtype and obtain marrow for cytogenetic and immunophenotypic studies. Cytogenetic, molecular, cytochemical, and immunophenotypic studies are important in diagnosing AML and defining major subtypes of AML in the FAB and WHO classifications.

Classification and Staging

The classification of AML has been revised by a group of pathologists and clinicians under the auspices of the World Health Organization (WHO). While elements of the French-American-British classification have been retained (i.e., morphology, immunophenotype, cytogenetics and clinical features), the WHO classification incorporates more recent discoveries regarding the genetics and clinical features of AML in an attempt to define entities that are biologically homogeneous and that have prognostic and therapeutic relevance. Each criterion has prognostic and treatment implications but, for practical purposes, antileukemic therapy is similar for all subtypes, except acute promyelocytic leukemia (M3).

As other malignancies, haematological malignancies do not have formal staging system. Their outcome is grouped according to various prognostic factors.

Prognostic factor

Cytogenetic analysis provides some of the strongest prognostic information available, predicting outcome of both remission induction and postremission therapy. Cytogenetic abnormalities that indicate a good prognosis include t(8; 21), inv(16) or t(16;16), and t(15;17). Normal cytogenetics portend average-risk AML. Patients with AML that is characterized by deletions of the long arms or monosomies of chromosomes 5 or 7; by translocations or inversions of chromosome 3, t(6; 9), t(9; 22); or by abnormalities of chromosome 11q23 have particularly poor prognoses with chemotherapy. These cytogenetic subgroups predict clinical outcome in older patients with AML as well as in

younger patients. Some genetic molecular markers like NPM1, FLT3, C-KIT, CEBPA mutation are useful prognostic factor.

Remission rates in adult AML are inversely related to age, with an expected remission rate of more than 65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age. Duration of remission may be shorter in older patients. Other adverse prognostic factors include central nervous system involvement with leukemia, systemic infection at diagnosis, elevated white blood cell count ($>100,000/\text{mm}^3$), treatment-induced AML, and history of myelodysplastic syndromes or another antecedent hematological disorder. Patients with leukemias that express the progenitor cell antigen CD34 and/or the P-glycoprotein (MDR1 gene product) have an inferior outcome. AML associated with an internal tandem duplication of the FLT3 gene (FLT3/ITD mutation) has an inferior outcome that is attributed to a higher relapse rate.

Treatment of acute myeloid leukemia (AML)

Advances in the treatment of AML have resulted in substantially improved complete remission rates. Treatment should be sufficiently aggressive to achieve complete remission because partial remission offers no substantial survival benefit.

Since myelosuppression is an anticipated consequence of both the leukemia and its treatment with chemotherapy, patients must be closely monitored during therapy. They must be treated by physicians experienced in these regimens at centers that are equipped to deal with potential complications. Facilities must be available for hematologic support with multiple blood fractions including platelet transfusions, as well as for the treatment of related infectious complications.

Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. About 50% of those who attain complete remission can be expected to survive 3 or more years and may be cured.

Treatment is divided into two phases:

- Remission induction (to attain remission) and
- Postremission (to maintain remission).

Maintenance therapy for AML is not recommended most current treatment other than for acute promyelocytic leukemia. postremission therapy appears to be effective when given immediately after remission is achieved.


Remission induction

Non M3 (Acute Promyelocytic Leukemia) AML

The two-drug regimen (7+3) of daunorubicin given in conjunction with cytarabine will result in a complete response rate of approximately 65%. The addition of etoposide or thioguanine has not shown improvement in response. The role of high-dose cytarabine in induction therapy is controversial.

AML arising from myelodysplasia or secondary to previous cytotoxic chemotherapy has a lower rate of remission than de novo AML. A retrospective analysis of patients undergoing allogeneic BMT in this setting showed that the long-term survival for such patients was identical regardless of whether or not patients had received remission induction therapy (disease-free survival was approximately 20%). These data suggest that patients with these subsets of leukemia may be treated primarily with allogeneic BMT if their overall performance status is adequate, potentially sparing patients the added toxic effect of induction chemotherapy.

Older adults who decline intensive remission induction therapy or are considered unfit for intensive remission induction therapy may derive benefit from low-dose cytarabine. The



complete remission rate and survival with low-dose cytarabine was better than hydroxyurea. Newer agents like Azacitidine or Decitabine had shown some improvement in response and survival in this subgroup of patients.

Supportive care during remission induction treatment should routinely include red blood cell and platelet transfusions when appropriate. Empiric broad spectrum antimicrobial therapy is an absolute necessity for febrile patients who are profoundly neutropenic. Careful instruction in personal hygiene, dental care, and recognition of early signs of infection are appropriate in all patients. Rapid marrow ablation with consequent earlier marrow regeneration decreases morbidity and mortality. Prophylactic oral antibiotics may be appropriate in patients with expected prolonged, profound granulocytopenia. Colony-stimulating factors have been studied in an effort to shorten the period of granulocytopenia associated with leukemia treatment. If used, these agents are administered after completion of induction therapy. Growth factor administration did not impact on mortality or on survival.

Acute Promyelocytic Leukemia

Special consideration must be given to induction therapy for acute promyelocytic leukemia (PML). Oral administration of All-trans-retinoic acid (ATRA); along with chemotherapy is the standard of care. ATRA is not effective in patients with AML that resembles M3 morphologically but does not demonstrate the t(15;17) or typical PML-RARα gene rearrangement. ATRA induces terminal differentiation of the leukemic cells followed by restoration of nonclonal hematopoiesis. Administration of ATRA leads to rapid resolution of coagulopathy in most patients. Administration of ATRA can lead to hyperleukocytosis as well as a syndrome of respiratory distress now known as the differentiation syndrome. Prompt recognition of the syndrome and aggressive administration of steroids can prevent severe respiratory distress.

Studies showed a disease-free survival benefit to maintenance therapy, which consisted of 6-mercaptopurine plus methotrexate, and intermittent ATRA.

The role of arsenic trioxide (ATO) in the management of previously untreated patients is also well established. It is showing promising results with low cost of therapy.

In APL, careful management of coagulopathy is required. Coagulopathy is occasionally a problem in patients undergoing induction with ATRA plus chemotherapy. This coagulopathy can lead to catastrophic intracranial bleeding.

Postremission therapy

Postremission therapy is always indicated in therapy that is planned with curative intent. Almost all patients who did not receive postremission therapy experienced a relapse after a short median complete remission duration.

Current approaches to postremission therapy include

- Short-term, relatively intensive chemotherapy with cytarabine-based regimens similar to standard induction clinical trials (postremission chemotherapy)
- Postremission chemotherapy with more dose-intensive cytarabine-based treatment, high-dose chemotherapy
- High-dose marrow-ablative therapy with autologous bone marrow rescue
- High-dose marrow-ablative therapy with allogeneic bone marrow rescue

Dose-intensive cytarabine-based chemotherapy can be complicated by severe neurologic and/or pulmonary toxic effects

and should be administered by physicians experienced in these regimens at centers that are equipped to deal with potential complications.

Allogeneic bone marrow transplantation (BMT) results in the lowest incidence of leukemic relapse, even when compared with BMT from an identical twin (syngeneic BMT). This has led to the concept of an immunologic graft-versus-leukemia effect, similar to (and related to) graft-versus-host disease. The improvement in freedom from relapse using allogeneic BMT as the primary postremission therapy is offset, at least in part, by the increased morbidity and mortality caused by graft-versus-host disease, veno-occlusive disease of the liver, and interstitial pneumonitis. The DFS rates using allogeneic transplantation in first complete remission have ranged from 45% to 60%. The use of allogeneic BMT as primary postremission therapy is limited by the need for a human leukocyte antigen (HLA)-matched sibling donor and the increased mortality from allogeneic BMT of patients who are older than 60 years. Presently, the mortality from allogeneic BMT that uses an HLA-matched sibling donor ranges from 10% to 20%. The use of matched, unrelated donors for allogeneic BMT is being evaluated at many centers but has a very substantial rate of treatment-related mortality, with DFS rates less than 35%. Retrospective analysis of data from the International Bone Marrow Transplant Registry suggests that postremission chemotherapy does not lead to an improvement in DFS or OS for patients in first remission undergoing allogeneic BMT from an HLA-identical sibling. In older and less fit patients reduced intensity conditioning regime (RIC) transplant offers better chances of survival. Umbilical cord blood transplant and haplo-identical (half-match) transplant can be considered where transplant is the only curative option.

Autologous BMT yielded DFS rates between 35% and 50% in patients with AML in first remission. Autologous BMT has also cured a smaller proportion of patients in second remission. Treatment-related mortality rates of patients who have had autologous peripheral blood or marrow transplantation range from 5% to 10%.

Good-risk factors include t(8; 21), inv(16) associated with M4 AML with eosinophilia, and t(15; 17) associated with M3 AML. Poor-risk factors include deletion of 5q and 7q, trisomy 8, t(6; 9), t(9; 22), and a history of myelodysplasia or antecedent hematologic disorder.

Patients in the good-risk group have a reasonable chance of cure with intensive postremission therapy, and it may be reasonable to defer transplantation in that group until early first relapse.

The poor-risk group is unlikely to be cured with postremission chemotherapy, and allogeneic BMT in CR1 is a reasonable option for patients with an HLA-identical sibling donor. However, even with allogeneic stem cell transplantation, the outcome for patients with high-risk AML is poor. The efficacy of autologous stem cell transplantation in the poor-risk group has not been reported to date but is the subject of active clinical trials.

Patients with normal cytogenetics are in an intermediate-risk group, and postremission management should be related allogeneic BMT in CR1 according to most of guidelines. Autologous BMT has shown benefit over chemotherapy alone in intermediate risk group patients where option of allogeneic BMT is not available.

Dr. Shishir Seth MD, DM,

Fellow Leukemia/ Bone Marrow Transplant (Vancouver-Canada)
Consultant- Hemato-Oncology & Bone Marrow Transplant

INFECTION PREVENTION WEEK

Infection control is a discipline that applies epidemiologic and scientific principles and statistical analysis to the prevention or reduction in rates of Nosocomial infections. In order to achieve the main goal of preventing or reducing the risk of hospital-acquired infections, an Infection prevention week was conducted in RGCI & RC, under the guidance of Dr Gauri Kapoor (Director Pediatric Hematology and Oncology) and Dr. Neelam Sachdeva (Sr. Consultant Microbiology) Target audience included doctors, technicians, nurses, housekeeping & security staff. Main emphasis was on Hand hygiene which is the single most important measure for the prevention of the spread of infection. The department for infection control was overwhelmed with the kind of response they got.

Posted at : Ashok Vihar Head Post Office, Delhi-110052
Registered with Registrar of Newspaper Under No. 68797/98
Postal Department Registration No. DL(N)/004/2012-14
Licensed to Post without prepayment under No. "U"(DN)-162/2012-14



RGCON - 2012

11th International Conference of
Rajiv Gandhi Cancer Institute & Research Centre

INTERNATIONAL PROSTATE CANCER SYMPOSIUM & LIVE OPERATIVE ROBOTIC WORKSHOP

(THEME: PROSTATE)



VENUE:

6th April 2012
Auditorium: PGIMER & Dr. RML Hospital, New Delhi
7th & 8th April 2012
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Contact Details

Dr. Sudhir Rawal

Organizing Secretary

Rajiv Gandhi Cancer Institute & Research Centre

Ph +91- 9810139757, +91-11-47022027

Email: drsudhir.rawal@gmail.com

Website : www.rgci.org

Dr. Samir Khanna

Co- Organizing Secretary

Rajiv Gandhi Cancer Institute & Research Centre

Ph- + 91-9899024255, +91-11-47022027

Email: drsamirkhanna@gmail.com

Website : www.rgci.org

Ms. Anju Chauhan

Coordinator (RGCON 2012)

Rajiv Gandhi Cancer Institute & Research Centre

Ph +91-9873155130 off:+91- 11-47022027

Email: bacchalanju@gmail.com

Website: www.rgci.org

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Printed & Published by Mr. K. K. Mehta on behalf of Indraprastha Cancer Society & Research Centre and Printed at Raju Art Printers, 18-A, Old Gobind Pura Extn., Street No.2, Parwana Road, Delhi-51, Tel. : 9871006333
Published from RGCI&RC, Sector-V, Rohini, New Delhi-110085 • Editor: Dr. A. K. DEWAN