

DO NOT WRITE ON THIS PACKET!

LEUKEMIA GROUP

INSTRUCTIONS: Complete the two attached **CALGB: 10102 (C-1005) Leukemia Follow-Up forms and two 10102(C-1006) Peripheral Blood and Bone Marrow Report forms** for the time periods listed below and answer the questions for each time period for this sample patient. In order to complete the response section on the forms, we need you to refer to the response section of the protocol provided and the pathology reports provided for you on this patient.

Study 10102

A

Patient ID# 111111 Patient Initials: (X., X.X.), Hospital ID# 56789 at Duke University Medical Center. The patient is alive and on Course I. The treatment course covered on the first form should be from 6/16/04 to 7/27/04. The last dose given was on 7/13/04. The patient did not receive Gleevec during the first course. The patient also did not have a transplant during this time period. The date the patient was known to be in remission or stable disease was 7/20/04.

Did the patient achieve a response during this time period?

If yes, what is the response and what is the date of response?

If the patient progressed, what is the site of progression?

What was the patient's best overall response to date?

B

Patient ID# 111111 Patient Initials: (X.,X.X.), Hospital ID# 56789 at Duke University Medical Center. The patient is alive and on Course VII. The treatment course covered on the second form should be from 3/30/05 to 11/1/05. The last dose given was on 4/26/05. The patient did not receive Gleevec during this course. The patient did not have a transplant during this time period.

Did the patient achieve a response during this time period?

If yes, what is the response and what is the date of response?

If the patient progressed, what is the site of progression?

What was the patient's best overall response to date?

Sex:M

BD:

MR#: 74800

Specimen Description

Jul 20, 2004 13:56

Surgical Pathology Report

Patient Name: [REDACTED]
Accession #: [REDACTED]
Med. Rec #: [REDACTED]
Submitting Physician: [REDACTED]

*****Clinical History*****
Preoperative diagnosis: 204.0, ALL.

*****Final Pathologic Diagnosis*****

- A. Bone Marrow; aspirate, biopsy, and peripheral blood:
- Hypercellular marrow (50%) without definitive morphologic or immunophenotypic evidence of precursor B cell acute lymphoblastic leukemia, (see comments).
 - Trilineage hematopoiesis with mild erythroid hyperplasia.
 - Increased stainable iron without ringed sideroblasts.

*****Comment*****

Differential count shows trilineage hematopoiesis with mild erythroid hyperplasia and no evidence of increased blasts. Core biopsy shows hypercellular bone marrow with trilineage hematopoiesis and erythroid predominance. Flow cytometry shows no definitive immunophenotypic evidence of increased population of blasts.

In summary; there is no definitive morphologic or immunophenotypic evidence of persistent precursor B cell acute lymphoblastic leukemia. Correlation with cytogenetics including FISH/molecular studies of translocation t(9;22) is recommended to rule out minimal residual disease.

The previous material, S04-27548 through S04-28586, is noted.

clm/LOZ:7/21/04
Electronically Signed By
7/21/04 16:07:41

*****MICROSCOPIC:*****

The following specimens were interpreted to arrive at the above diagnosis:
>

CBC data and smear review:

WBC: 9.9 x K/uL; Hgb: 10.4 g/dL; Hct: 29.6%; MCV: 88.6 fl; RDW: 17.6%; Plt: 243 K/uL

Manual differential: bands 17%, neutrophils 73%, lymphocytes 7%, monocytes 2%, eosinophils 1%, basophils 0%, 2 nRBC/100 WBC.

Blood smear interpretation: Review of the blood smear shows normocytic anemia with mild polychromasia and 2+ anisocytosis. The leukocytes are adequate in number and show unremarkable differential and no evidence of circulating blasts. Platelets are adequate in number and show normal morphology.

Bone marrow aspirate smear differential (500 cells):

Blasts: 2%

Promyelocytes: 1%

Myelocytes: 9%

Metamyelocytes: 4%

Bands/neutrophils: 36%

Lymphocytes: 7%

Monocytes: 4%

Eosinophils: 1%

Basophils: <1%

Erythroid: 36%

Plasma cells: <1%

Cellularity: The bone marrow shows a cellularity of 50%.

M: E Ratio: The myeloid to erythroid ratio is 1.52:1.

Erythropoiesis: Erythroid hyperplasia with mild megaloblastoid change. Rare forms with nuclear contour irregularities and nuclear blebs are noted (<5% of the erythroid cells)

Granulopoiesis: Adequate myelopoiesis with orderly maturation to the neutrophil stage.

Megakaryocytes: Megakaryocytes are present in adequate numbers with unremarkable morphology.

Lymphocytes/plasma cells: The lymphocytes/plasma cells are unremarkable. Blasts are not increased.

Iron Stain: Stainable iron is increased, ringed sideroblasts are not seen.

Other: The bony trabeculae are unremarkable.

Flow cytometric analysis: There is no immunophenotypic evidence of an abnormal population of cells.

*****SPECIMEN(S) RECEIVED:*****

Bone marrow, biopsy

*****GROSS DESCRIPTION:*****

The specimen is received in one properly labeled container with the patient's name and accession number.

CALGB-DMC
JAN 31 2005

Specimen Description

Sex:

BD:

Nov 01, 2005 15:38

Surgical Pathology Report

Patient Name:
Accession #:
Med. Rec #:
Submitting Physician:

****Clinical History****

Preoperative diagnosis: Evaluate disease. ICD code 204.0.

****Final Pathologic Diagnosis****

- A. Bone marrow; aspirate, touch preparation and biopsy:
 - Hypercellular marrow (60%) with relapsed precursor B cell acute lymphoblastic leukemia, (see comments).
 - Decreased trilineage hematopoiesis.

****Comment****

Morphologic and immunophenotypic findings are c/w relapsed precursor B cell acute lymphoblastic leukemia. Correlation with cytogenetics is recommended.

The previous material S04-27548 through CY05-1804 is noted.

bab/LOZ:11/2/05

Electronically Signed By

11/2/05 18:29:32

****MICROSCOPIC:****

CBC data and smear review: 11/1/05
WBC: 2.2 x K/uL; Hgb: 13.2 g/dL; Hct: 38.3%; MCV: 109.0 fl; RDW: 16.0%;
Plt: 47 K/uL
Electronic differential: neutrophils 62.8%, lymphocytes 30.5%, monocytes 3.6%, eosinophils 2.8%, basophils 0.3%

Blood smear interpretation: Review of blood smear shows leukopenia with absolute neutropenia. Circulating blasts are not seen. The red cells are macrocytic. There is a moderate thrombocytopenia with normal morphology.

CAICB-DMC
DEC 27 2005

Bone marrow aspirate smear differential (500 cells):

Blasts: 44%
Promyelocytes: 4%
Myelocytes: 2%
Metamyelocytes: 6%
Bands/neutrophils: 9%
Lymphocytes: 12%
Monocytes: 2%
Eosinophils: 1%
Basophils: <1%
Erythroid: 18%
Plasma cells: 2%

Cellularity: The bone marrow shows a cellularity of 60%.

M:E Ratio: The myeloid to erythroid ratio is not applicable.

Erythropoiesis: Erythroid hypoplasia with normoblastic maturation.

Granulopoiesis: Myeloid hypoplasia with preserved maturation to the granulocyte stage.

Megakaryocytes: Megakaryocytes are present in decreased numbers with unremarkable morphology.

Lymphocytes/plasma cells: Differential count shows markedly increased blasts. The blasts are medium sized with high N/C ratio, round nuclei with immature chromatin and variably prominent nucleoli. Auer rods are not seen. Core biopsy shows hypercellular bone marrow with sheets of immature cells c/w blasts. Plasma cells and lymphocytes are unremarkable.

Iron Stain: Iron staining can not be evaluated due to aspicular specimen. No ringed sideroblasts are seen.

Flow cytometric analysis: Flow cytometric analysis demonstrates an abnormal population of blasts (34%) with expression of CD10+, CD19+, CD20+ subset faint (15%), CD45+ faint/negative and HLA-DR. The blasts are negative for CD34, surface immunoglobulin light chains Kappa and lambda and all myeloid markers analyzed.

*****SPECIMEN(S) RECEIVED:*****

Bone marrow, biopsy

*****GROSS DESCRIPTION:*****

The specimen is received in one properly labeled container with the patient's name and accession number.

A. The specimen is designated "bone marrow biopsy" and consists of one fragment of tan-brown firm tissue which is 1.1 cm in length x 0.1 cm in diameter. Cassette A1 is submitted for decalcification. TE 1

Lab Use Only: Job ID 353185

Gross description by: A. August

CALGB 10102

2. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim or sargramostim) must be documented and reported on flow sheets.
3. If filgrastim or sargramostim are used, they must be obtained from commercial sources, unless otherwise specified in the protocol.

11.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

The June 1974 modification of the CALGB criteria for evaluating acute leukemia will be used. Criteria for evaluating bone marrow is available in Appendix IA, while criteria for evaluating peripheral blood is available in Appendix IB.

The assessment of response after treatment for acute leukemia requires a physical examination, complete blood count, platelet count, differential count, and bone marrow aspiration and biopsy. Extramedullary sites known to be involved by leukemia prior to treatment (e.g., mediastinal lymphadenopathy or CSF) must be reexamined as well. Immunophenotyping, cytochemistry, and cytogenetic analyses are supportive data but are not required for clinical assessment. The **response must be maintained for one month** in order to be valid; patients who proceed with additional chemotherapy must have no evidence of disease recurrence during this one month interval.

Investigators are cautioned that the bone marrow cytology and peripheral blood differential count in patients who are recovering from chemotherapy or who have received hematopoietic growth factors or cytokines may be shifted to immaturity, reflecting regenerating hematopoiesis; this should not be misinterpreted as residual or recurrent leukemia. Whenever the initial morphological result is ambiguous, a second bone marrow examination should be performed \geq one week later, and confirmatory data should be gathered from cytogenetic analyses, immunophenotyping, or cytochemistry.

11.1 Complete Remission (CR):

A CR requires the following: an absolute neutrophil count (segs and bands) $> 1500/\mu\text{l}$, no circulating blasts, platelets $> 100,000/\mu\text{l}$; bone marrow cellularity $> 20\%$ with trilineage hematopoiesis, and $< 5\%$ marrow blast cells, none of which appear neoplastic. All previous extramedullary manifestations of disease must be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement). The response must be maintained for at least 4 week. If patients continue on with treatment, there can be no evidence of recurrence of ALL for at least 4 weeks.

11.2 Complete Remission with Incomplete Hematologic Recovery: satisfies all CR criteria except an absolute neutrophil count (segs and bands) $< 1500/\mu\text{L}$ and/or platelets $< 100,000/\mu\text{L}$.

11.3 Partial Remission (PR):

A PR requires all of the CR criteria except that the marrow may still contain 5-25% leukemia blast cells. Even if $< 5\%$ blasts were present, the response is a PR if Auer rods or blast cells with obvious leukemia morphology (e.g., lymphoblasts) were present.

CALGB 10102

11.4 Refractory/Progressive Disease:

Failure to achieve a CR or PR with persistence of leukemia cells after treatment.

11.5 Relapsed Disease:

The reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%) or in any other extramedullary site after a CR; or progression to >25% leukemia blasts cells in the marrow after a PR. In the case of isolated CNS relapse (positive cytopspin examination of CSF), please refer to Section 7.10.4 and consult with the Study Chair.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

12.1 Duration of Treatment

Day on Study	Clinical Status*	Action
I-29	M ₀ , M ₁ , M ₂ , M ₃	Continue treatment. Patients with M ₃ marrow may be removed from protocol therapy or may proceed to Course II (at treating physician's discretion).
II-29	M ₀ , M ₁ M ₂ , M ₃ , marrow relapse	Continue treatment. Remove from protocol therapy (allogeneic BMT if possible, see Section 12.3).
III-43	M ₀ , M ₁ M ₂ , M ₃ , marrow relapse	Continue Treatment. Remove from protocol therapy (allogeneic BMT if possible, see Section 12.3).
VII-29	M ₀ , M ₁ M ₂ , M ₃ , marrow relapse	Continue treatment. Remove from protocol therapy (allogeneic BMT if possible, see Section 12.3).

* If marrow cellularity is inadequate for diagnosis, repeat weekly until determination can be made.

12.1.1 M₀ or M₁: Continue treatment or follow-up as specified in the protocol and observe for marrow relapse (see Section 12.1.3).

12.1.2 Failure to achieve M₁ or better by Day II-29, or if bone marrow relapse: Remove patient from protocol therapy. Refer for allogeneic bone marrow transplantation if possible (see Section 12.3). **Alternatively, patients with an M₃ marrow on Day I-29 may proceed to receive Course II (see Sections 7.2.3 and 7.3.4).**

12.1.3 Relapse

Patients who achieve complete remission (M₀, M₁) will continue on protocol therapy until the appearance of hematologic relapse as defined by:

1. One bone marrow aspirate with $\geq 20\%$ or more lymphoblasts and leukemia cells present.
2. Two or more marrow aspirates which show progressive repopulation with lymphoblast and leukemia cells in excess of 10% culminating in 25% or more.
3. At the time of documented marrow relapse, submit peripheral blood and marrow specimens for CALGB 9665 (mandatory) and 9862 (mandatory). Patients enrolled on CALGB 8461 require submission of bone marrow specimens.

FORMULAS AND CONVERSIONS

Absolute Granulocyte Count = WBC x % (neutrophil = segs + bands)

Example:

WBC = 2.2×10^3 Neutrophils: Segs 61% + Bands 4% = 65

Formula: $2200 \times .65 = 1430$ or 1.43×10^3

Absolute Lymphocyte Count = WBC x % (lymphocytes)

Example:

WBC = 4.5×10^3 Lymphocytes = 10

Formula: $4500 \times .10 = 450$ or 0.45×10^3