CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Instructions for Juvenile Myelomonocytic Leukemia Post-HCT Data (Form 2115)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the JMML Post-HCT Form.

E-mail comments regarding the content of the CIBMTR Forms Instruction Manual to: CIBMTRFormsManualComments@nmdp.org. Comments will be considered for future manual updates and revisions. For questions that require an immediate response, please contact your transplant center's CIBMTR CRC.

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Juvenile Myelomonocytic Leukemia Post-HCT Data

Juvenile Myelomonocytic Leukemia (JMML) is a cancer of the white blood cells. It is characterized by overproduction of myelocytes and monocytes; this chronic proliferation of myelocytes and monocytes in the bone marrow prevents the formation of healthy red blood cells, white blood cells, and/or platelets. Since JMML is characterized both by dysregulation and excessive proliferation of the bone marrow, it is classified as a mixed myelodysplastic-myeloproliferative disorder. The pathologic features of JMML are believed to primarily be the result of a clonal abnormality leading to activation of Ras signaling; this inappropriate activation of Ras leads to over-proliferation of certain cell types. Approximately 75% of all JMML patients carry one of three mutually exclusive mutations associated with inappropriate Ras activation: direct *RAS* mutations, *NF1*-inactivating mutations, or protein tyrosine phosphatase, non-receptor type 11 (PTPN11) mutations.[1]

Clinically, JMML presents as hepatosplenomegaly with or without lymphadenopathy, pallor, fever, and rash. Due to the broad differential diagnosis associated with this presentation, a diagnosis of JMML may require a very

extensive work-up. JMML most commonly affects children less than six years of age, with most patients diagnosed at less than two years of age. It comprises less than 2% of all childhood leukemias, and has historically carried a grim prognosis, with less than 10% survival with a chemotherapy-only approach.[1] With HCT, survival approaches 50%.[2]

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track whose primary disease is reported on the Form 2400, question 357, as Myelodysplastic (MDS)/myeloproliferative (MPN) diseases and question 480 as Juvenile Myelomonocytic Leukemia (JMML/JCML). The Juvenile Myelomonocytic Leukemia Post-HCT Data (Form 2115) must be completed in conjunction with each Post-HCT follow-up form (Forms 2100, 2200, 2300) completed. The form is designed to capture specific data occurring within the timeframe of each reporting period (i.e., between day 0 and day 100 for Form 2100, between day 100 and the six-month date of contact for Form 2200, between the date of contact for the six-month follow up and the date of contact for the one-year follow up for Form 2200, etc.).

For recipients who had JMML that transformed to AML prior to transplant, it is only necessary to complete Form 2110 (Acute Myelogenous Leukemia Post-HCT Data). Although form 2015 (Juvenile Myelomonocytic Leukemia Pre-HCT Data) is required to obtain JMML data pre-HCT, Form 2115 (Juvenile Myelomonocytic Leukemia Post-HCT Data) is not required for these recipients.

[1]National Cancer Institute. Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ®), Health Professionals version. Accessed at: http://www.cancer.gov/cancertopics/pdq/treatment/childAML/HealthProfessional Accessibility verified on August 8, 2013.

[2]Locatelli F, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. *Blood.* 2004;105(1):410-419.

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.
- Outcomes data accurately reflects appropriate transplant type and product for each transplant center.
- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other agency.

The Key Fields precede the form body and are automatically populated in the FormsNet3^{SM} application based on information provided on the CRID Assignment Form 2804. If errors are noted in the key fields, correct Form 2804 and then review it for accuracy. After Form 2804 has been corrected, verify data

has been updated on all completed forms. If the data has not been updated automatically, centers will need to reprocess the completed forms to correct the key field data. If errors are noted in key fields for second or subsequent transplants, contact your CRC to make any necessary corrections to the transplant or product type. Transplant and product type will not be automatically populated on product or donor specific forms (Forms 2004, 2005, and 2006) and will need to be manually reported.

Disease Assessment at the Time of Best Response to HCT

Question 1: Compared to the disease status prior to the preparative regimen, what was the best response to HCT since the date of the last report? (Include response to any therapy given for post-HCT maintenance or consolidation, but exclude any therapy given for relapsed, persistent, or progressive disease.)

Any specified therapy administered post-HCT to prolong remission or for minimal residual disease is considered part of the HCT and should be included when assessing the recipient's response to transplant. Treatment given post-HCT for relapsed or persistent disease is not considered part of the HCT and should be excluded when assessing the response to HCT. If treatment was given post-HCT for relapsed or persistent disease, assess the patient's best response *prior* to the start of that treatment. If therapy was only given for reasons other than relapsed or persistent disease, assess the patient's best response throughout the entire duration of the reporting period.

If the recipient was in remission at the start of the preparative regimen, indicate "continued complete remission" and continue with question 4.

If the recipient did not achieve CR prior to the start of the preparative regimen, specify their best response following transplant and continue with question 2.

Table 1. Disease status criteria for JMML

DISEASE STATUS	DEFINITION
Complete Remission (CR)	Normalization of WBC and resolution of organomegaly.
Partial Remission (PR)	≥ 50% reduction of WBC from maximum pre-treatment value and/or ≥ 50% reduction of organomegaly from pre-treatment maximum

Table 1. Disease status criteria for JMML *(cont.)*

DISEASE STATUS	DEFINITION
Marginal Response (MR)	25-50% reduction of WBC from maximum pre-treatment value and 25-50% reduction of organomegaly from pre-treatment maximum *or* ≥ 50% reduction of WBC from maximum pre-treatment value and *no change* in organomegaly *or* ≥ 50% reduction of organomegaly from pre-treatment maximum and *no change* in WBC
Stable Disease (SD)	≤ 25% reduction of WBC from maximum pre-treatment value and/or ≤ 25% reduction of organomegaly from pre-treatment maximum
Progressive Disease (PD)	Increase in WBC and/or organomegaly
Relapse	Reappearance of disease characteristics such as leukocytosis, absolute monocytosis, and organomegaly after complete remission (CR)
Progression to AML	≥ 20% blasts in the bone marrow or peripheral blood

Question 2: Was the date of best response previously reported?
If the patient achieved their best response in the current reporting period, indicate "no" and continue with question 3.

If the recipient achieved their best response during a previous reporting period, indicate "yes" and continue with question 4.

Question 3: Date assessed
Indicate the date best response was achieved. Report the date of the pathological evaluation (e.g., bone marrow biopsy), blood/serum assessment (e.g., CBC, peripheral blood smear), radiographic evaluation (e.g., abdominal CT), or physical examination (e.g., organomegaly on palpation). Enter the date the sample was collected for pathological and/or laboratory evaluations.

Relapse or Progression Post-HCT

Question 4: Has the disease relapsed or progressed since the date of last report?
Report if the recipient had a hematologic or clinical relapse at any time during the reporting period. Progression is defined as an increase in WBC and/or

organomegaly *or* transformation to AML. Relapse is defined as the reappearance of disease characteristics after a complete remission. Do not report relapse or progression for the reappearance of molecular or cytogenetic abnormalities associated with the patient's disease in the absence of clinical evidence of disease.

If no assessments were consistent with relapse or progression during the reporting period, indicate "no" and continue with question 11.

Question 5: Date of disease relapse/progression
Report the date of the assessment consistent with relapse or progression. If relapse or progression was identified by hematologic assessment, report the date the specimen was collected.

Questions 6-10: Specify site(s) of disease relapse/progression
Indicate "yes" or "no" for each site specified in questions 6-9. Do not leave any responses blank. Specify only the sites of clinical or hematologic disease; cytogenetic and molecular evidence of disease does not need to be specified. If "yes" is indicated for "other site," specify the site in question 10. At least one of questions 6-9 must be answered "yes."

Post-HCT Therapy

Question 11: Was any therapy given for relapsed, persistent, or progressive disease since the date of last report?
Indicate if the recipient received treatment for relapsed JMML during the current reporting period. Do not report therapy given for maintenance (to prolong remission or for minimal residual disease). If the patient received therapy for relapsed, persistent, or progressive disease, check "yes" and continue with question 12. If the patient did not receive therapy, or only received therapy for maintenance, check "no" and continue with question 21.

Question 12: Systemic therapy
Systemic therapy refers to a delivery mechanism where a therapeutic agent is delivered orally or intravenously, enters the bloodstream, and is distributed throughout the body.

Indicate "yes" if the patient received systemic and continue with question 12. If the patient did not receive systemic therapy, indicate "no" and continue with question 17.

Questions 13-16: Specify systemic therapy agent(s)
Indicate "yes" or "no" for each drug administered for therapy during the current reporting period for reasons relapse, progressive, or persistent disease. Do not

leave any responses blank. If the recipient received an agent that is not listed, check “yes” for “other systemic therapy” and specify the treatment in question 16.

Question 17: Donor cellular infusion
A donor cellular infusion, or DCI, is a form of immunotherapy that is commonly used for a variety of purposes, including the treatment of refractory or recurrent disease. In the setting of relapsed, persistent, or progressive disease, the DCI is used to create a graft-versus-leukemia/tumor (GVL/GVT) effect. In general, the recipient does not receive a preparative regimen prior to receiving the additional donor cells since replacement of the marrow is not the goal.

Indicate “yes” if the patient received one or more donor cellular infusion(s); also report the DCI on the corresponding Form 2100, 2200, or 2300. If the patient did not receive a donor cellular infusion, check “no.”

Question 18: Subsequent HCT
An HCT is an infusion of a product (i.e., bone marrow, peripheral blood stem cells, cord blood, etc.) that contains CD34+ cells. Refer to Appendix O for further clarification on defining a subsequent HCT.

The intention of an HCT is to restore hematopoiesis and immunity. It is usually preceded by a preparative regimen used to both reduce disease burden and prevent rejection of the new stem cells by killing normal and malignant cells, if present. In some cases, a preparative regimen might not be used prior to the infusion of CD34+ cells, but this would still be considered an HCT.

A subsequent HCT may be administered to replace or repopulate the recipient’s marrow and reconstitute the immune system. If the recipient receives a subsequent HCT as treatment for relapsed disease, check “yes” and continue with question 19. Only report a subsequent HCT given for relapsed, persistent, or progressive disease. If a subsequent HCT is reported in question 18, it must also be reported on the corresponding Form 2100, 2200, or 2300.

If a recipient receives a subsequent HCT between the HCT follow-up time points (100 day, six months, annually), the comprehensive report form sequence will start over with another Pre-TED Form (2400), Recipient Baseline Data Form (2000), and Juvenile Myelomonocytic Leukemia Pre-HCT Data Form (2015). However, if the recipient receives an autologous HCT as a result of a poor graft or graft failure, the comprehensive report form sequence **will not** start over if the preceding HCT was also autologous. Generally this type of infusion (autologous rescue) is used to treat the recipient’s poor graft response, rather than to treat the recipient’s disease.

Question 19: Other therapy

If the patient received a therapy that is not listed, indicate "yes" and specify the therapy in question 20. If the patient did not receive another therapy not listed, check "no."

Disease Status at the Time of Evaluation for this Reporting Period

Question 21: What was the disease status?

Indicate the disease status of JMML as of the last evaluation during the reporting period.

Table 2. Disease status criteria for JMML

DISEASE STATUS	DEFINITION
Complete Remission (CR)	Normalization of WBC and resolution of organomegaly.
Partial Remission (PR)	≥ 50% reduction of WBC from maximum pre-treatment value and/or ≥ 50% reduction of organomegaly from pre-treatment maximum
Marginal Response (MR)	25-50% reduction of WBC from maximum pre-treatment value and 25-50% reduction of organomegaly from pre-treatment maximum *or* ≥ 50% reduction of WBC from maximum pre-treatment value and *no change* in organomegaly *or* ≥ 50% reduction of organomegaly from pre-treatment maximum and *no change* in WBC
Stable Disease (SD)	≤ 25% reduction of WBC from maximum pre-treatment value and/or ≤ 25% reduction of organomegaly from pre-treatment maximum
Progressive Disease (PD)	Increase in WBC and/or organomegaly
Relapse	Reappearance of disease characteristics, such as leukocytosis, absolute monocytosis, and organomegaly after complete remission (CR)
Progression to AML	≥ 20% blasts in the bone marrow or peripheral blood
Not assessed	No assessment of leukocytosis or organomegaly was done at any time during the reporting period.

Question 22: Date assessed
Enter the date of the most recent assessment establishing disease status within the reporting period. The date reported should be that of the most disease-specific assessment within a reasonable timeframe of the date of contact (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and/or laboratory evaluations, the date the imaging took place for radiographic assessments, or the date of physical examination.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Signature
The FormsNet3^{SM} application will automatically populate the signature data fields, including name and email address of person completing the form and date upon submission of the form.