Disease Response
What Are We Looking For?

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Objectives

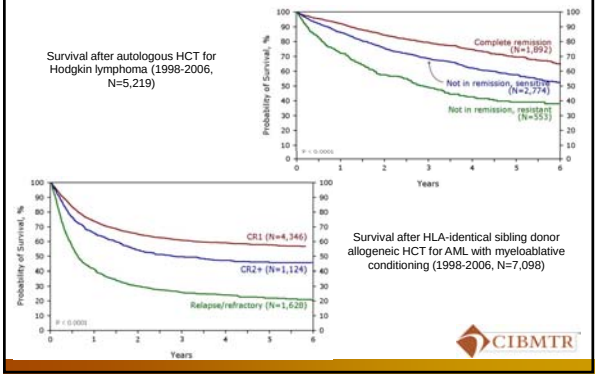
- Review importance of disease response in CIBMTR research
- Review examples of disease response criteria for CML and lymphomas

Disease Response = Outcomes

- One of the most important endpoints for transplant research studies
- Correlates with overall HCT outcomes and survival
- Used to classify other outcomes (e.g. treatment related mortality)
- Accurate assessment of pre-HCT response is also very important

Pre-HCT Response and HCT Outcomes

Survival after autologous HCT for Hodgkin lymphoma (1998-2006, N=5,219)



Survival after HLA-identical sibling donor allogeneic HCT for AML with myeloablative conditioning (1998-2006, N=7,098)

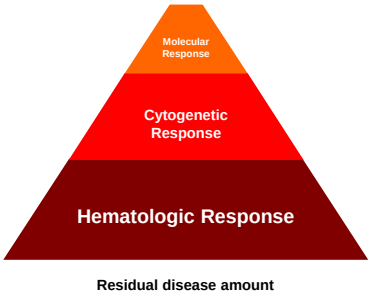
CIBMTR

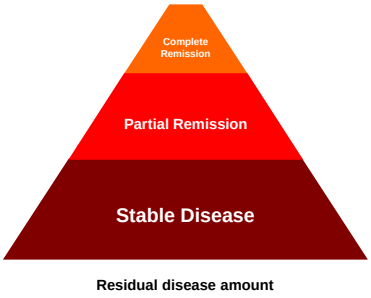
Accurate Assessment of Disease Response is Crucial to CIBMTR Studies

Response Reporting Is Not (Always) Easy

- Response criteria can be ambiguous
- Many acceptable response criteria may be available
- Response criteria can change with time

General Definitions





Hematologic Response/Remission

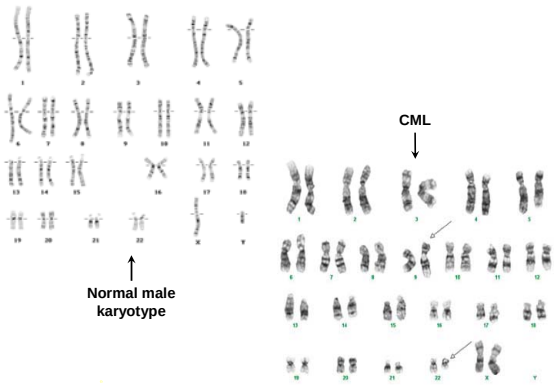
- Generally used for ALL, AML and CML
- Absence of disease in the peripheral blood
- Absence of disease in the bone marrow (on routine morphology and stains)

Cytogenetic Response/Remission

- Generally used for ALL, AML and CML
  - May also be used for other diseases (e.g. myeloma, CLL, lymphoma)
- Chromosomal abnormalities are evaluated
- Two common methods
  - Chromosomal banding
  - FISH

Chromosomal Banding

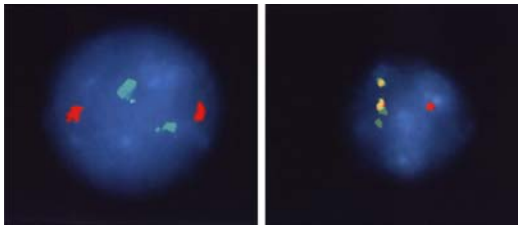
- Also called 'routine cytogenetics'
  - Cell division is arrested in metaphase stage
  - Chromosomes are stained using dyes
  - Advantage – entire genome is viewed
  - Disadvantage – labor intensive, only detects major abnormalities



FISH

- Fluorescent in-situ hybridization
  - Fluorochrome labeled DNA probe is applied to cells – visualized by fluorescence microscopy
- Advantage – better resolution, more sensitive and specific, straightforward test
- Disadvantage – identifies abnormality specific to the probe applied, cannot identify other abnormalities

FISH for CML

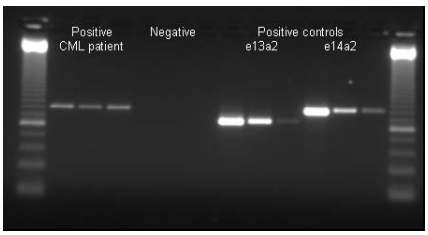


Normal CML

Molecular Response/Remission

- Generally used for CML
  - May also be used for other diseases (e.g. ALL, AML, CLL, lymphoma)
- DNA is evaluated
- Polymerase chain reaction (PCR)
  - Most frequently used molecular test
  - DNA is amplified many fold
  - Amplified DNA can be analyzed further (e.g. gel electrophoresis)
  - Extremely sensitive

PCR for CML



Complete/Partial Response

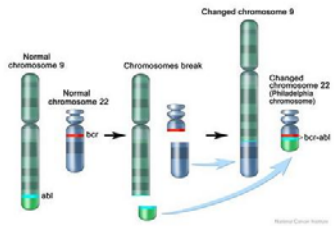
- Used for diseases that can be 'measured'
  - Myeloma, lymphoma, CLL
- Assessed by blood tests (e.g. M-protein) or imaging studies (e.g. CT or PET)

Examples

CML

CML

- Characteristic feature is Philadelphia chromosome t(9;22) → leads to formation of BCR-ABL



Diagnosis and Disease Assessment

- Peripheral blood and/or bone marrow counts and morphology
- Cytogenetics for t(9;22)
  - Chromosome banding from bone marrow
  - FISH for t(9;22) from blood or bone marrow
- Molecular testing for BCR-ABL
  - Qualitative or quantitative PCR
  - PCR's from different labs are not always comparable

CML Natural History

- Three disease phases
  - Chronic phase
  - Accelerated phase
    - Many criteria (MD Anderson, Sokal, WHO)
  - Blast phase (>20% blasts)
- Patients can go from accelerated or blast phase to chronic phase (2nd or greater chronic phase)

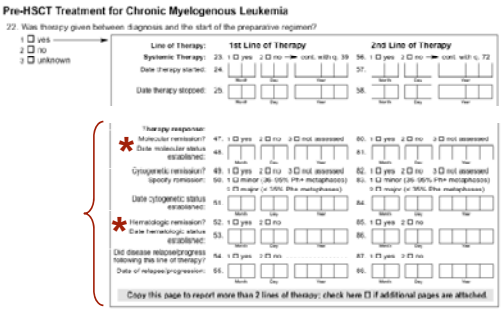
Response Criteria for CML

- Complete hematologic response or remission (all must be present)
  - Platelet count <450,000/uL
  - WBC count <10,000/Ul
  - No immature neutrophils
  - <5% basophils
  - Spleen not palpable

Cytogenetic and Molecular Response

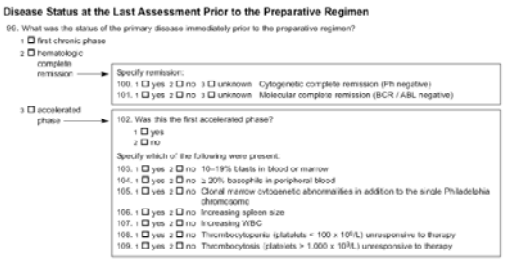
- Cytogenetic response/remission
  - No response - >95% Ph+ cells
  - Minor response – 36-95% Ph+ cells
  - Major response – <35% Ph+ cells
  - Complete response – no Ph+ cells
- Molecular response/remission
  - Major response - >3 log reduction
  - Complete response – no BCR-ABL transcript detectable

Form 2012 (Pre-HSCT, CML)



* Complete hematologic remission or complete molecular remission

Form 2012 (Pre-HSCT, CML)



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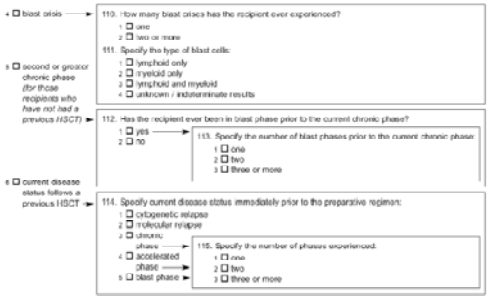
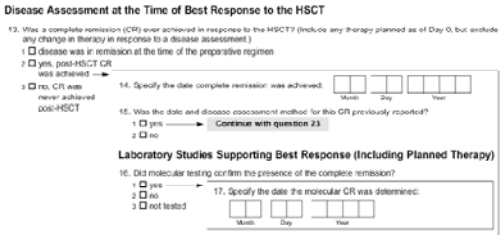
Form 2012 (Pre-HSCT, CML)



Form 2112 (Post-HSCT, CML)



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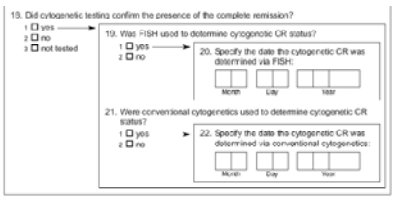
Form 2112 (Post-HSCT, CML)



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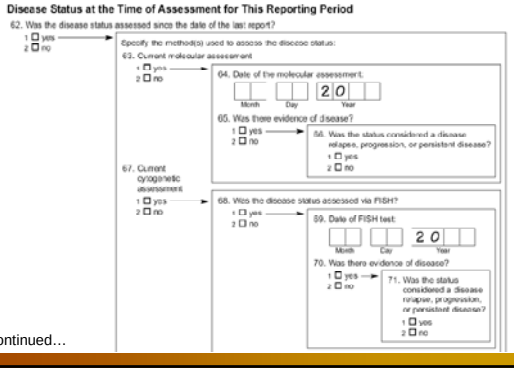

Disease Status at the Time of Assessment for This Reporting Period

62. Was the disease status assessed since the date of the last report?
1 ☐ yes → Specify the method(s) used to assess the disease status:
2 ☐ no

63. Current molecular assessment
1 ☐ yes → 64. Date of the molecular assessment: Month Day 20 Year
2 ☐ no

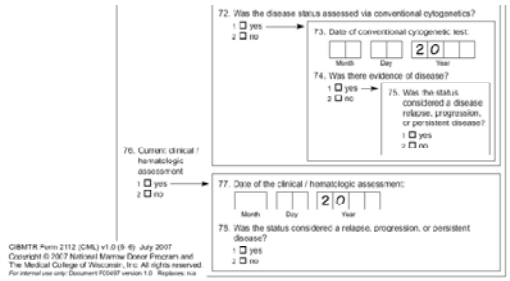
65. Was there evidence of disease?
1 ☐ yes → 66. Was the status considered a disease relapse, progression, or persistent disease? 1 ☐ yes 2 ☐ no
2 ☐ no

67. Current cytogenetic assessment
1 ☐ yes → 68. Was the disease status assessed via FISH?
2 ☐ no
1 ☐ yes → 69. Date of FISH test: Month Day 20 Year
2 ☐ no

70. Was there evidence of disease?
1 ☐ yes → 71. Was the status considered a disease relapse, progression, or persistent disease? 1 ☐ yes 2 ☐ no
2 ☐ no

Continued…

Form 2112 (Post-HSCT, CML)


72. Was the disease status assessed via conventional cytogenetics?
1 ☐ yes → 73. Date of conventional cytogenetic test: Month Day 20 Year
2 ☐ no

74. Was there evidence of disease?
1 ☐ yes → 75. Was the status considered a disease relapse, progression, or persistent disease? 1 ☐ yes 2 ☐ no
2 ☐ no

76. Current clinical / hematologic assessment
1 ☐ yes → 77. Date of the clinical / hematologic assessment: Month Day 20 Year
2 ☐ no

78. Was the status considered a relapse, progression, or persistent disease?
1 ☐ yes
2 ☐ no

CIBMTR Form 2112 (CML) v1.0 (9-6) July 2007
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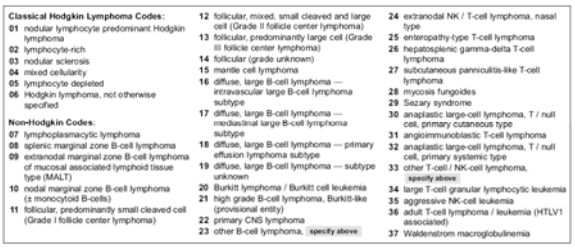
Hodgkin and Non-Hodgkin Lymphoma

Lymphomas

- Malignant hematologic disorders characterized by involvement of:
  - Lymph nodes
  - Bone marrow
  - Occasionally, peripheral blood and other sites
- Response assessment can be challenging
  - Many lymphoma types with varying presentation and patterns of response

Large Number of Lymphoma Types


Classical Hodgkin Lymphoma Codes:
01 nodular lymphocyte predominant Hodgkin lymphoma
02 lymphocyte-rich
03 nodular sclerosis
04 mixed cellularity
05 lymphocyte depleted
06 Hodgkin lymphoma, not otherwise specified

Non-Hodgkin Codes:
07 lymphoplasmacytic lymphoma
08 splenic marginal zone B-cell lymphoma
09 extranodal marginal zone B-cell lymphoma of mucosal associated lymphoid tissue type (MALT)
10 nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
11 follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)
12 follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma)
13 follicular, predominantly large cell (Grade III follicle center lymphoma)
14 follicular (grade unknown)
15 mantle cell lymphoma
16 diffuse, large B-cell lymphoma — intravascular large B-cell lymphoma subtype
17 diffuse, large B-cell lymphoma — mediastinal large B-cell lymphoma subtype
18 diffuse, large B-cell lymphoma — primary effusion lymphoma subtype
19 diffuse, large B-cell lymphoma — subtype unknown
20 Burkitt lymphoma / Burkitt cell leukemia
21 high grade B-cell lymphoma, Burkitt-like (provisional entity)
22 primary CNS lymphoma
23 other B-cell lymphoma, specify above
24 extranodal NK / T-cell lymphoma, nasal type
25 enteropathy-type T-cell lymphoma
26 hepatosplenic gamma-delta T-cell lymphoma
27 subcutaneous panniculitis-like T-cell lymphoma
28 mycosis fungoides
29 Sezary syndrome
30 anaplastic large-cell lymphoma, T / null cell, primary cutaneous type
31 angioimmunoblastic T-cell lymphoma
32 anaplastic large-cell lymphoma, T / null cell, primary systemic type
33 other T-cell / NK-cell lymphoma, specify above
34 large T-cell granular lymphocytic leukemia
35 aggressive NK-cell leukemia
36 adult T-cell lymphoma / leukemia (HTLV1 associated)
37 Waldenstrom macroglobulinemia

Form 2018

Diagnosis and Disease Assessment

- Lymph node aspiration or biopsy
- Peripheral blood counts and morphology
- Bone marrow morphology
- Flow cytometry
- Cytogenetics
- Molecular testing
- Imaging

Cytogenetics and Molecular Testing

- Chromosome banding/FISH or PCR can be done for chromosomal abnormalities or gene fusion products
  - T-cell NHL: t(2;5) → ALK/NPM genes
  - Burkitt's NHL: t(8;14) → MYC/IGH
  - Follicular NHL: t(14;18) → IGH/BCL2
  - Mantle cell NHL: t(11;14) → IGH/CCND1

Flow Cytometry

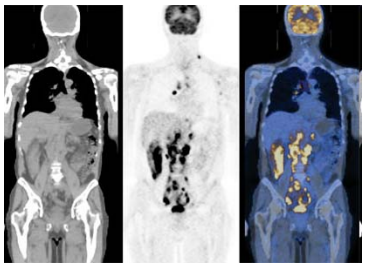
- Stream of cells can be manipulated (e.g. tagged with fluorescent dye) and passed through a laser beam
  - Cells can be separated for counting and analysis
- Positive result usually correlates with bone marrow morphology findings
  - Residual small (<2%) B-cell clone on flow cytometry only in absence of other findings → unclear significance

Imaging for Staging Lymphoma

- Computed tomography (CT)
- Positron emission tomography (PET)
  - ^{18}F-glucose (FDG) radio isotope is used → avidly taken up by lymphoma
  - More sensitive than CT scan
  - Different types have varying PET avidity (diffuse large B-cell, Hodgkin's, follicular, mantle cell lymphoma are PET avid)
- MRI for assessment of specific sites (e.g. central nervous system)

PET-CT

- Combines PET scan and CT scan



CT PET PET-CT

Lymphoma Response Criteria

- Complete remission
  - No clinical evidence of disease
    - Typically PET avid lymphomas: post-therapy residual mass of any size should be PET negative
    - Variably PET avid lymphomas: all lymph nodes normal size by CT
  - No palpable liver or spleen
  - Bone marrow biopsy should be negative

Cheson et al, J Clin Oncol, 2007:25; 579

Lymphoma Response Criteria

- Partial remission
  - ≥50% decrease in lymph node size and/or hepatic/splenic nodules (sum of the product of diameters)
  - Typically PET avid lymphomas: PET positive in at least one previous site
  - No new sites of disease

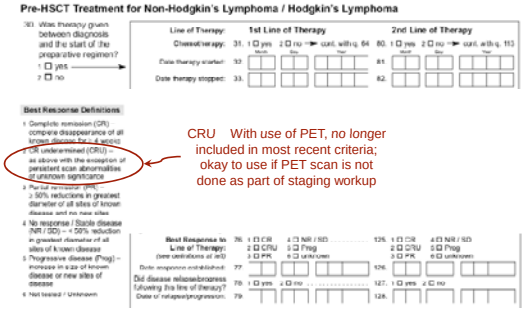
Lymphoma Response Criteria

- Stable disease
  - Failure to attain CR/PR or progressive disease
  - Typically PET avid lymphomas: PET positive at prior sites of disease, no new sites of disease

Lymphoma Response Criteria

- Progressive disease or relapse
  - Appearance of new lesions (lymph node, bone marrow or other sites)
  - 50% increase in lymph node size
  - Increase in PET uptake

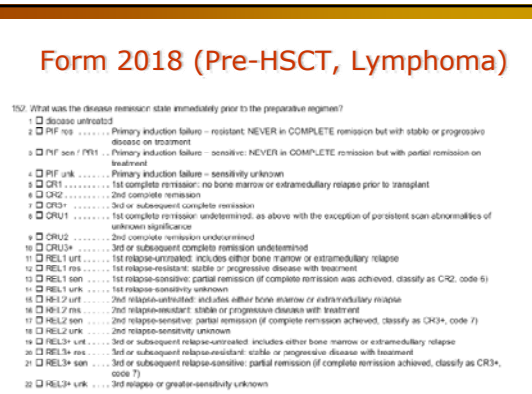
Form 2018 (Pre-HSCT, Lymphoma)



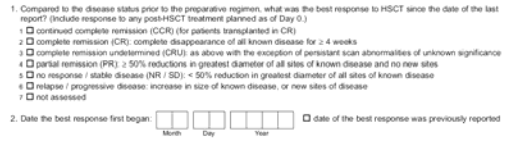
Form 2018 (Pre-HSCT, Lymphoma)

* Primary induction failure (PIF): failure to achieve CR or PR with any pre-HSCT therapy; Sensitive/resistant: response to chemotherapy (if CR/PR → sensitive disease)

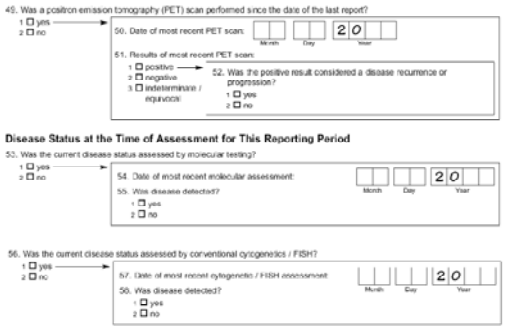
Form 2018 (Pre-HSCT, Lymphoma)



Form 2118 (Post-HSCT, Lymphoma)



Form 2118 (Post-HSCT, Lymphoma)



Troubleshooting

Not Sure How to Report Response?

- Ask your center director or physician taking care of patient
- Contact us!!
  - Provide us with documentation to determine appropriate response

Response in Long-term Survivors

- Staging studies (e.g. CT, PET, bone marrow) may not be repeated
- If no clinical evidence of disease (e.g. history and physical exam) → can classify as continuing complete remission

Remember…

- Accurate reporting of response (pre and post-HCT) is very important for CIBMTR research studies

QUESTIONS?