Myeloid Malignancies

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Executive Summary

Beginning on February 1, 2014, the World Trade Center (WTC) Health Program will consider blood or bone marrow disorders of the myeloid line to be slow-growing blood cancers. Accordingly, they will be considered WTC-related health conditions, making them available for WTC Health Program medical treatment services for eligible members. These cancers had been considered non-malignant by the Administrator because they were referred to as "pre-leukemic" hematopoietic disorders in the medical literature. Recent scientific advances, however, characterize these "pre-leukemic" myeloid neoplasms as slow-growing blood cancers, and authoritative scientific sources now consider them to be malignant myeloid neoplasms.

After receiving a request from the WTC Clinical Centers of Excellence to review certain myeloid disorders in terms of their status as malignancies,[1] the WTC Health Program has determined that, in addition to types of leukemias, these myeloid malignancies are eligible for coverage by the WTC Health Program as WTC-related health conditions.[2] The group of myeloid malignancies includes the following health conditions:

(1) Myelodysplastic Syndromes (MDSs);
(2) Myeloproliferative neoplasms (MPNs);
(3) Myelodysplastic/myeloproliferative neoplasms (MDS/MPN); and
(4) Myeloid malignancies associated with eosinophilia and abnormalities of growth factor receptors derived from platelets or fibroblasts.[3]

[1] Letter to Drs. Dori Reissman and John Halpin of the WTC Health Program from World Trade Center Clinical Centers of Excellent Principal Investigators dated December 16, 2013 (on file at WTC Health Program).

[2] See 42. C.F.R. § 88.1 (Table 1).

[3] Acute myeloid leukemia (AML) remains eligible for coverage as a WTC-related health condition because it is already included in the List of WTC-Related Health Conditions. See 42 C.F.R. § 88.1 (Table 1).

I. Introduction

In December of 2013 the WTC Clinical Centers of Excellence (CCEs) requested that the WTC Health Program review certain myeloid disorders in terms of their status as malignancies.[1] MDS is one type of a group of myeloid malignancies. Therefore, based on the CCEs' request, the Administrator reviewed the available scientific literature and authoritative disease classification sources pertaining to the malignancy of myeloid neoplasms.

The term "myeloid" includes all cells belonging to the granulocyte (i.e., neutrophil, eosinophil, basophil), monocyte/macrophage, erythroid, megakaryocyte, and mast cell lineages. Myeloid malignancies are clonal diseases of hematopoietic stem or progenitor cells.[4] These malignancies can be present in the bone marrow and peripheral blood. They result from genetic and epigenetic alterations that perturb key processes such as self-renewal, proliferation and impaired differentiation.[5,6]

Some myeloid disorders, such as the myeloid leukemias, have long been considered malignant while other myeloid disorders have been considered non-malignant or pre-leukemia blood disorders which may become malignant over time. However, recent scientific findings indicate that these "pre-leukemia" blood disorders are actually forms of slow-growing blood cancers. [7,8]

Based on the morphology, cytochemistry, immunophenotype, genetics, and clinical features of myeloid disorders, the World Health Organization (WHO) categorizes myeloid malignancies into five primary types: (1) acute myeloid leukemia; (2) myelodysplastic syndromes (MDS); (3) myeloproliferative neoplasms (MPN); (4) myelodysplastic and myeloproliferative (MDS/MPN) neoplasms; and (5) myeloid neoplasms associated with eosinophilia and abnormalities of growth factor receptors derived from platelets or fibroblasts. The types and subtypes of myeloid malignancies are identified in Table 1 in the Appendix.

[4] Murati A, Brecqueville M, Devillier R, Mozziconacci M, Gelsi-Boyer V, Birnbaum D [2012]. Myeloid malignancies: mutations, models and management. BMC Cancer 12:304-325.

[5] Shih AH, Abdel-Wahab O, Patel JP, Levine RL [2012]. The role of mutations in epigenetic regulators in myeloid malignancies. Nat Rev Cancer 12(9):599-612.

[6] Ntziachristos P, Mullenders J, Trimarchi T, Aifantis I [2013]. Mechanisms of epigenetic regulation of leukemia onset and progression. Adv Immunol 117:1-38.

[7] Ma X [2012]. Epidemiology of myelodysplastic syndromes. Am J Med. 125(7 Suppl): S2–S5.

[8] Tefferi A, Vardiman JW [2008]. Classification and diagnosis of myleoproliferative neoplasms: the World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 22:14-22.

II. Risk Factors

A. Myelodysplastic Syndrome and Myeloproliferative Neoplasms

The primary risk factor for MDS is age. The majority of secondary MDS cases occur after treatment for other cancers with radiation therapy or chemotherapy that employs alkylating agents or topoisomerase inhibitors. In addition, several environmental and/or occupational exposures have been associated with increased rates of MDS or cytogenetic abnormalities associated with MDS including pesticides[9], benzene[10], organic solvents[11], semi-metals[12], and inorganic dusts[13].

Studies of occupations identified increased incidence of MPN among poultry workers, commercial pressmen, petroleum refinery workers, agricultural workers, cooks/waiters and clerks. Studies of associations with exposure to chemicals such as benzene, petroleum solvents, hair dyes, and pesticides have produced inconsistent results.[14]

B. Myeloid Malignancies Other Than AML, MDS and MPN

Information on associations of environmental or occupational exposures for other myeloid malignancies was not found in a Medline search of the relevant medical literature.

[9] Vundinti BR, Kerketta L, Jijina F, Ghosh K [2009]. Cytogenetic study of Myelodysplastic syndrome from India. Indian J Med Res 130:155-159.

[10] Corey SJ, Minden MD, Barber DL, et al. [2007]. Myelodysplastic syndromes: the complexity of stem-cell diseases. Nat Rev Cancer 7:118-129.

[11] Rigolin GM, Cuneo A, Roberti MG, Bardi A, Bigoni R, Piva N, Minotto C, Agostini P, De Angeli C, Del Senno L, Panedda R, Castoldi G [1998]. Exposure to myelotoxic agents and myelodysplasia: case-control study and correlation with clinicobiological findings. Br J Haematol 103:189-197.

[12] West RR, Stafford DA, White AD, Bowen DT, Padua RA [2000]. Blood 95:2093-2097.

[13] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellstrom-Lindberg E, Tefferi A, Bloomfield CD [2009]. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114:937-951.

[14] Reviewed by: Anderson LA, Duncombe AS, Hughes M, Mills ME, Wilson JC, McMullin MF [2012]. Environmental, lifestyle, and familial/ethnic factors associated with myeloproliferative neoplasms. Am J Hematol 87(2):175-182.

III. Clinical and Pathologic Features

The clinical and pathologic features of myeloid malignancies vary according to type.

Acute myeloid leukemia. AML results from the clonal expansion of myeloid blasts in the peripheral blood, bone marrow or other tissue. It is caused when either the myeloid stem cells produce abnormal myeloblasts which do not become healthy white blood cells or too many myeloid stem cells become abnormal red blood cells or platelets. As a result, leukemic blasts, or immature cell forms, accumulate in the bone marrow, peripheral blood, and occasionally in other tissues, and the production of normal red blood cells, platelets, and mature granulocytes are reduced a variable amount. The increased production of malignant cells, along with a reduction in these mature elements, results in a variety of systemic consequences including anemia, bleeding, and an increased risk of infection.[13]

Myelodysplastic syndromes. MDSs are a spectrum of bone marrow failure disorders that share the common pathologic feature of cytological dysplasia. They progress to acute myeloid leukemia (AML) in about 30% of patients. MDSs are classified according to features of cellular morphology, cellular and molecular genetics, immunophenotyping, etiology, and clinical presentation. The seven subtypes of MDSs are listed in Table 1 in the Appendix.

The morphological classification of MDSs is largely based on the percent of myeloblasts in the bone marrow and blood, the type and degree of myeloid dysplasia, and the presence of ring sideroblasts. MDSs remain among the most challenging of the myeloid malignancies to diagnose and classify, particularly in cases in which the blast percentage is not increased in the peripheral blood or bone marrow.[13]

Myeloproliferative Neoplasms. MPNs are clonal hematopoietic stem cell disorders characterized by proliferation of one or more of the myeloid lineages. The subtypes of myeloproliferative malignancies are identified in Table 1.

Each of these disorders involves dysregulation at the multipotent hematopoietic stem cell (CD34) and clonal myeloproliferation and the absence of dyserythropoiesis, dysgranulopoiesis and monocytosis. Abnormal proliferation among this type arises from specific genetic rearrangements or mutations affecting protein tyrosine kinases or related molecules which produce constitutively active signal transduction pathways.[15,16]

[15] Kittur J, Knudson RA, Lasho TL, Finke CM, Gangat N, Wolanskyj AP, Li C, Wu W, Ketterling RP, Pardanani A, Tefferi A [2007]. Clinical correlates of JAK2V617F allele burden in essential thrombocythemia. Cancer 109:2279–2284.

[16] De Keersmaecker K, Cools J [2006]. Chronic myeloproliferative disorders: a tyrosine kinase tale. Leukemia. 20:200–205.

Among the subtypes of MPN, chronic myelogenous leukemia (CML) is defined by its causative molecular lesion, the BCR-ABL fusion gene, which most commonly results from the Philadelphia translocation (Ph). Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are the three main Ph-negative myeloproliferative neoplasms. The cardinal features of the main myeloproliferative neoplasms are an elevated white blood cell count in CML, increased red-cell mass in PV, a high platelet count in ET, and bone marrow fibrosis in PMF.[13,17]

Myelodysplastic/myeloproliferative neoplasms. MDS/MPNs are clonal myeloid disorders that possess both dysplastic and proliferative features but are not properly classified as either myelodysplastic syndromes (MDS) or chronic myeloproliferative disorders (CMPD). The MDS/MPN category includes myeloid neoplasms with clinical, laboratory, and morphologic features that overlap MDS and MPN. These disorders commonly have mutations in the genes that encode the RAS or MAPK dependent signaling pathways.[13]

Myeloid neoplasms associated with eosinophilia and abnormalities of growth factor receptors derived from platelets or fibroblasts. These malignancies arise by forming abnormal fusion genes that encode altered surface or cytoplasmic proteins that activate signal transduction pathways.[13,18] The subtypes of myeloid neoplasms associated with eosinophilia and abnormalities of platelet or fibroblast growth factor receptors are listed in Table 1 in the Appendix. Although eosinophilia is characteristic of each subtype, the clinical presentation of each subtype varies.[13,19]

IV. Classification

The WTC Health Program uses the International Classification of Diseases Version 9 (ICD-9) coding system for carcinogenic and non-carcinogenic health condition classification. Under the ICD-9 coding system, myelodysplastic and myeloproliferative neoplasms are considered pre-leukemia blood disorders, and therefore were not considered by the WTC Health Program as malignancies. However, since the ICD-9 coding system was developed by the WHO, substantial scientific progress has been made in understanding the behavior of these malignancies. As a result, these health conditions—formerly classified not to be malignancies — are now consider to be

[17] Anastasi J [2009]. The myeloproliferative neoplasms: insights into molecular pathogenesis and changes in WHO classification and criteria for diagnosis. Hematol Oncol Clin North Am 23(4):693-708.

[18] Savage N, George TI, Gotlib J [2013]. Myeloid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, and FGFR1: a review. Int J Lab Hematol 35(5):491-500.

[19] Gotlib J, Cools J [2008]. Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias. Leukemia 22(11):1999-2010.

malignancies in the newer coding systems such as the International Classification of Diseases for Oncology (ICD-O), which is used for cancer classifications by cancer registries and by the ICD-9 replacement, ICD-10.

In 2000, the World Health Organization (WHO) changed the behavior code for myelodysplastic and myeloproliferative conditions in the ICD-O from 1 (i.e., "uncertain whether benign or malignant") to 3 (i.e., "malignant"). Based on the underlying science that led to the changes in the ICD-O coding system, these neoplasms became reportable to population-based cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) Program in 2001.

In 2008, the WHO updated the *Classification of Tumours of the Haematopoietic and Lymphoid Tissues*, a worldwide consensus of hematologic malignancies. The WHO classification system uses the available information on morphology, cytochemistry, immunophenotype, genetics, and clinical features to define clinically meaningful diseases. In this classification system myeloid neoplasms are characterized as malignant.

In making decisions on coverage of myeloid neoplasms, the WTC Health Program is decreasing its reliance on older disease classification systems, such as the ICD-9 coding system, and increasing its reliance on newer authoritative sources, such as ICD-O and ICD-10 coding systems. In addition the WTC Health Program is increasing its reliance on mature scientific information available in the published literature whose significance has been widely acknowledged. This changed emphasis will allow the WTC Health Program to make certification decisions based on more current scientific information.

V. Incidence of Myeloid Malignancies

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and accounts for approximately 80 percent of cases in this group.[20] The incidence increases from about 1.3 per 100,000[21] for those under to 65 to about 12.2 cases per 100,000 for those over 65 years [Siegel 2012]. The age-adjusted incidence rate for acute myeloid leukemia in the years 1975–2003 was 3.7 per 100,000 persons.[22,23]

[20] In children less than 10 years of age AML accounts for less than 10 percent of acute leukemias.

[21] All incidence rates reported here are age-adjusted to the 2000 U.S. Standard Population (19 age groups-Census P25-1130).

[22] SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

[23] Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010,

The other myeloid neoplasms occur at much lower frequencies, but individual incidence rates for each type have not been published. The combined age-adjusted incidence rate for MDSs, MPNs and chronic myelomonocytic leukemia for 2006-10 was 7.8 per 100,000 persons.[22,24] All other myeloid malignancies are very rare, and their precise incidence is unknown at this time.

However, based on the reported incidence of the malignant myeloid malignancies in general, it is reasonable to assume that the combined age-adjusted incidence rate for all myeloid malignancies in the U.S. is less than 15 per 100,000 persons.

VI. Summary of Evidence

Recent scientific advances and authoritative classification sources characterize myeloid neoplasms as slow-growing blood cancers or malignancies. Based on this evidence, the WTC Health Program considers MDSs, MPNs, MDS/MPN, and myeloid neoplasms associated with eosinophilia and abnormalities of growth factor receptors derived from platelets or fibroblasts, to be eligible for coverage under the rare cancers category of covered WTC-related health conditions. Acute myeloid leukemia (AML) is eligible for coverage because it is included in the List of WTC-related health condition.

VII. Certification of Myeloid Malignancies for WTC Health Program Coverage

The WTC Health Program bases coverage decisions for cancer on the WHO disease classification systems. However, classification systems change over time, and even the latest classification systems may not be based on the most recent scientific evidence and diagnostic criteria that contribute to identifying conditions. Consequently, the WTC Program Administrator has determined that reliance on classification systems can inappropriately constrain the decisions of the WTC Health Program and can result in undesired denial of coverage.

Two conditions which have been affected by the reliance on classification systems are Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPN). These disorders had been considered pre-leukemia blood disorders and were not classified as malignant conditions. However, they demonstrate clonal proliferation behavior which is

National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

[24] SEER 18 areas (San Francisco (SF), Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta (ATL), San Jose-Monterey (SJM), Los Angeles (LA), Alaska Native Registry, Rural Georgia (RG), California, excluding SF/SJM/LA, , Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).

a characteristic used to distinguish between benign and malignant conditions, and the scientific evidence indicates they should be considered forms of slow-growing blood cancers.

To inform certification decisions of myeloid neoplasms the WTC Health Program will use authoritative sources, such as the WHO disease classification system, and mature scientific information available in the published literature whose significance has been widely acknowledged. The WTC Health Program considers MDS, MPN, MDS/MPN, and myeloid neoplasms associated with abnormalities of growth factor receptors to be malignant cancers which can be covered under the rare cancers category of covered WTC-related health conditions. AML is listed as a covered WTC-related health condition.

When a physician from the Clinical Center of Excellence, or the Nationwide Provider Network, determines a neoplasm to be a "myeloid malignancy", the WTC Health Program will consider the myeloid malignancy for certification as a type of leukemia or as a "rare cancer."

Each determination of a myeloid neoplasm/malignancy as a WTC-related health condition must be considered for certification under (1) the minimum latency requirements for lymphoproliferative and hematopoietic cancers (including all types of leukemia and lymphoma),[25] and (2) the exposure requirements specified by the WTC Health Program in the WTC-3 Certification Request form.

[25] WTC Health Program. *Minimum Latency & Types or Categories of Cancer* (May 1, 2013). http://www.cdc.gov/wtc/pdfs/wtchpminlatcancer2013-05-01.pdf

APPENDIX

Table 1. The 2008 World Health Organization classification scheme for myeloid neoplasms .[A]

1. Acute myeloid leukemia

2. Myelodysplastic syndromes (MDS)

- 2.1 Refractory cytopenia with unilineage dysplasia
  - Refractory anemia; Refractory neutropenia; Refractory thrombocytopenia
- 2.2 Refractory anemia with ring sideroblasts
- 2.3 Refractory cytopenia with multilineage dysplasia
- 2.4 Refractory anemia with excess blasts-1
- 2.5 Refractory anemia with excess blasts-2
- 2.6 Myelodysplastic syndrome with isolated del(5q)
- 2.7 Myelodysplastic syndrome, unclassifiable

3. Myeloproliferative neoplasms (MPN)

- 3.1 Chronic myelogenous leukemia
- 3.2 Polycythemia vera
- 3.3 Essential thrombocythemia
- 3.4 Primary myelofibrosis
- 3.5 Chronic neutrophilic leukemia
- 3.6 Chronic eosinophilic leukemia, not otherwise categorized
- 3.7 Hypereosinophilic syndrome
- 3.8 Mast cell disease
- 3.9 MPNs, unclassifiable

4. Myeloplastic/myeloproliferative neoplasms (MDS/MPN)

- 4.1 Chronic myelomonocytic leukemia
- 4.2 Juvenile myelomonocytic leukemia
- 4.3 Atypical chronic myeloid leukemia
- 4.4 MDS/MPN, unclassifiable

5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFR-A or -B, or FGFR1

- 5.1 Myeloid neoplasms associated with PDGFRA rearrangement
- 5.2 Myeloid neoplasms associated with PDGFRB rearrangement
- 5.3 Myeloid neoplasms associated with FGFR1 rearrangement
  - (8p11 myeloproliferative syndrome)

[A] Adapted from: Tefferi A, Vardiman JW [2008]. Classification and diagnosis of myleoproliferative neoplasms: the World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia* 22:14-22.