Minimal Residual Disease as a Surrogate Endpoint in Hematologic Cancer Trials

Discussion Guide

Introduction

In the last two decades, advances in cancer research and drug development have transformed the cancer care landscape. Certain cancers that were once rapidly fatal can now be managed more like a chronic disease, and patients can experience many months or even years of remission. However, these advances have also created challenges to the rapid development of new therapies. As patients live longer, cancer trial timelines lengthen, as it can take longer to measure whether a treatment has a meaningful impact on survival. One of the key strategies for addressing this challenge and accelerating patient access to new therapies is the development and validation of surrogate endpoints that can be used to measure potential patient benefit at an earlier stage.

For drugs intended to treat hematologic cancers, ‘minimal residual disease’ (MRD) is one candidate surrogate endpoint that could be used to develop evidence of efficacy for regulatory review. Between 2012 and 2014, the US Food and Drug Administration (FDA) convened a series of workshops to address issues in MRD detection and use in four cancers: multiple myeloma (MM), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML).\(^{1,2,3,4}\) Though substantial progress has been made since that time in developing the evidence to support the use of MRD as a diagnostic and clinical tool in each of these cancers, questions remain over how best to move forward in terms of its validation as a surrogate endpoint that can be used to support regulatory review. In light of these issues, and under a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy is convening this public workshop to assess the current state of evidence available to support validation of MRD as a surrogate endpoint and advance the discussion of its use in developing new treatments for MM, CLL, ALL, and AML.

Background on Hematologic Malignancies

Hematologic cancers—which include leukemia, lymphoma, and myeloma—affect the blood, bone marrow, or lymphatic system. They are among the most common types of cancer and are the second leading cause of cancer death. An estimated 1.2 million people in the US are either living with or are in remission from hematologic malignancies, and an estimated 58,320 people are expected to die from blood cancer in 2016.\(^5\) Though treatment options have expanded in recent years, hematologic cancer represents a disease area with substantial unmet needs in patient care. Although there are many similarities among hematological cancers, each have unique molecular and pathophysiological features that affect disease pathology, prognosis, and testing and treatment considerations.

Multiple Myeloma

Myeloma is a disease of the bone marrow that manifests in the abnormal development of plasma cells. If left untreated, the mutated cells multiply and crowd out healthy plasma and stem cells in the bone marrow, which can compromise the immune system, weaken the bones, and lead to kidney damage.
The vast majority of myeloma cases are classified as multiple myeloma, because plasma cell tumors develop in bones at multiple sites.\(^4\)

Myeloma predominantly affects people over age 50, and African Americans are more than twice as likely to be diagnosed with the disease as whites. African Americans also experience worse outcomes compared to whites, though the reasons for these disparities are not clearly understood.\(^7\) There is no cure, though treatments are available to reduce symptoms, slow disease progression, provide prolonged remissions, and lengthen survival. In 2016, an estimated 30,330 cases of myeloma will be diagnosed, and 12,650 will die from the disease. Between 2006 and 2012, the 5-year survival rate for multiple myeloma was 48.5 percent.\(^8\)

**Chronic Lymphocytic Leukemia**

CLL develops in part from damage to DNA of the stem cells in the bone marrow (known as an “acquired mutation”). When additional environmental or epigenetic effects occur, bone marrow stem cells can transform into leukemic cells. These leukemic cells do not die at the same rate, and eventually crowd out normal blood cells. This in turn can cause anemia, interfere with blood clotting, and compromise an individual’s immune system. In some patients, the lymph nodes and spleen may enlarge and interfere with the function of the gastrointestinal and urinary tracts.

CLL is the most common form of leukemia in the Western hemisphere, and occurs almost exclusively in adults, most of whom are elderly. In 2013, an estimated 119,386 people in the United States were living with or in remission from the disease.\(^9\) Stem cell transplantation can be curative, and treatments are available to slow the growth of leukemic cells, lengthen remission, improve survival, and alleviate symptoms. From 2006-2012, the 5-year survival rate for CLL was 82.6%.\(^10\)

**Acute Lymphoblastic Leukemia**

As with CLL, ALL results in part from acquired mutations in the DNA of bone marrow stem cells, which leads to their uncontrolled growth into “lymphoblasts” or “leukemic blasts” that crowd out normal blood cell production and function.\(^11\) However, ALL progresses more rapidly than CLL. In addition to symptoms associated with CLL, ALL patients can suffer from organ damage, stroke, cardiac arrest, shortness of breath, body and headaches, and small red bleeding spots under the skin called petechiae.

ALL is the most common form of leukemia in children, and roughly 60 percent of cases occur in individuals under 20, with incidence of the disease peaking between 1 and 4 years of age. Treatment options include chemotherapy, stem cell transplantation, radiation therapy, and immunotherapy. An estimated 6,590 new cases will be diagnosed in 2016, and an estimated 1,430 will die.\(^12\) The survival rate of pediatric ALL is approximately 90 percent, but is substantially lower in adults, ranging from 20-40 percent.\(^13,14\)

**Acute Myeloid Leukemia**

The origins and symptoms of AML are similar to those of CLL and ALL, though people with AML can also suffer from swollen gums, an enlarged liver, and myeloid sarcoma (a tumor that forms outside of the marrow). AML is also more heterogeneous than either CLL or ALL, encompassing many genetic subtypes that can impact both prognosis and treatment options.\(^15,16\)
Although AML can occur at any age, adults aged 60 years and older are more likely to develop the disease than younger people. About 19,950 new cases of AML are expected to be diagnosed in the United States in 2016, and an estimated 10,430 will die of the disease.\(^\text{17}\) Though adults are more likely to be diagnosed with AML than are children, survival rates in children are significantly better. Under current treatment regimens, about 80 percent of children with AML achieve remission, with just more than half of those who achieve remission being considered “cured.” From 2005-2011, the overall 5-year survival rate of AML was 26 percent, but for children under 15 it was 66.5 percent.\(^\text{18}\)

**Minimal Residual Disease: Role in Evaluating Treatment of Hematologic Malignancies**

For clinical trials of new therapies for hematologic malignancies, the standard endpoints have included measures such as overall survival (OS), progression-free survival (PFS), event-free survival, or response rate.\(^\text{19,20}\) Over the last two decades, however, the introduction of novel therapies to treat these diseases has significantly improved clinical outcomes, leading to higher rates of remission, longer remissions, and better survival rates.\(^\text{21}\) As these outcomes improve, the amount of time required to measure endpoints like OS and PFS also increases, leading to longer, more expensive clinical trials. From 2004 to 2014, the average length of phase II oncology trials increased by roughly one year, while the length of phase III trials rose from 3.5 to almost 5 years.\(^\text{22}\) For this reason, there is significant interest in identifying and validating new surrogate endpoints that can be measured at an earlier stage, and which could be used to support faster clinical development and regulatory review of innovative new therapies.

At the same time, technologic advances in molecular testing have enabled the detection of leukemic cells with much greater accuracy, thus improving assessments of how deeply patients respond to a given therapy or combination of therapies. Accurate measurement of these remaining cells—referred to as minimal residual disease—can potentially be used to guide decision-making across a range of contexts. In certain clinical care settings, for example, MRD status can enable better treatment decisions, allowing physicians to assess a patient’s prognosis, identify patients who are at risk of relapse, or determine if they have responded well enough that they no longer require treatment. However, there are ongoing questions over how and to what extent MRD assessment should be integrated into routine clinical care, as the strength of the evidence base to support its use in guiding treatment decisions varies across hematologic cancer types and patient populations.\(^\text{23,24,25,26}\)

MRD is also widely used in clinical trials of hematologic cancer therapies, particularly as a prognostic biomarker that can be used to assess the risk of relapse and to stratify patients into different treatment arms.\(^\text{27,28,29,30}\) Studies have also found that MRD status correlates with endpoints like PFS and OS across a range of testing strategies and hematologic cancer subtypes, which has created substantial interest in validating MRD as a surrogate endpoint that could be used to support regulatory approval of new therapies.

However, the process of validating a surrogate endpoint is more complicated than demonstrating a simple correlation between a surrogate such as MRD and a clinical outcome like OS. The treatment effect on the surrogate must be shown to reliably and precisely predict the treatment effect on the corresponding clinical endpoint, and this must be demonstrated across multiple clinical trials. Furthermore, even when a surrogate has been validated in a particular context, it is not necessarily
appropriate to extrapolate that determination of validity to another disease, population, or therapeutic context.\textsuperscript{31}

The existing evidence to support the validity of MRD as a surrogate endpoint varies considerably across hematologic cancer subtypes, owing in part to the underlying molecular and pathophysiological differences between these diseases. A further challenge in validating MRD as a surrogate endpoint is the lack of standardization in how MRD status is measured, both between individual studies and across different institutions, which limits the ability to compare study outcomes or draw meaningful conclusions between studies.\textsuperscript{32} Collaborative efforts to standardize these various methods are underway, though progress varies across cancer subtypes and the specific methodologies used.\textsuperscript{33}

**Regulatory Efforts to Accelerate Drug Development for Hematologic Malignancies**

FDA has long recognized the importance of biomarkers in improving and accelerating the drug development process. Facilitating regulatory review of biomarkers was a key commitment for FDA under the fifth reauthorization of the Prescription Drug User Fee Act, and Section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 enhanced the agency’s authority to expedite the development of new treatments through its accelerated approval program.\textsuperscript{34} First instituted in 1992, the accelerated approval program allows FDA to provisionally approve a drug that is intended to treat a serious condition based on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit.\textsuperscript{35} Sponsors are then required to confirm this benefit through post-market trials. FDASIA expanded this approval pathway by authorizing FDA to include consideration of pharmacologic and other evidence generated using biomarkers or other innovative methods and tools when assessing whether an endpoint meets the standards necessary for accelerated approval.\textsuperscript{36} Since the passage of FDASIA, FDA has approved more than a dozen therapies for hematologic cancer alone based on a surrogate endpoint.\textsuperscript{37}

Over the last several years, FDA has also issued guidance on the development and use of biomarkers in medical product development, engaged the stakeholder community through public meetings, established a voluntary submission process for pharmacogenomic data, and, most recently, developed a formal stand-alone qualification program for biomarkers. Qualification is a formal conclusion that, within a defined context of use, a biomarker can be relied upon to have a specific interpretation and application in medical product development and regulatory review. Once a biomarker has been fully qualified, it can be used in multiple medical product development programs without the need to collect additional data to support its use within the defined context.

Between 2012 and 2014, the agency also co-sponsored a series of public workshop focused specifically on the potential role of MRD as a surrogate endpoint in MM, CLL, AML, and ALL.\textsuperscript{38,39,40,41} These workshops provided a platform for a range of regulatory, academic, and industry stakeholders to explore the status of MRD assessment within each of the four targeted cancers, highlight the technical and practical considerations for standardizing MRD detection, and identify the required next steps for validating MRD as a surrogate within each disease context. Since that time, substantial investment and progress has been made towards addressing the challenges and evidentiary gaps that were identified. However, there are ongoing questions over how best to approach the statistical validation of MRD as a
surrogate endpoint, and several scientific and practical barriers remain towards the broader use of MRD across these four cancers.

**Workshop Objectives and Questions for Discussion**

The objectives for today’s workshop are to: 1) discuss the regulatory background for use of MRD as a surrogate endpoint for regulatory decisions; 2) discuss the statistical basis for demonstrating and validating surrogacy; and 3) present the evidence available to support the use of MRD as a surrogate endpoint in clinical trials for new treatments in MM, CLL, ALL, and AML.

**Opening Presentations**

**Objectives:** Summarize the regulatory perspective on surrogate endpoints in hematological cancer treatment and in vitro diagnostics, provide an overview of prior FDA workshops related to MRD, and discuss the major biostatistical considerations for demonstrating surrogacy.

- **Presentation 1:** Surrogate Endpoints in Regulatory Decision-Making: The FDA Perspective
- **Presentation 2:** In Vitro Diagnostics in Hematologic Cancer
- **Presentation 3:** Major Biostatistical Considerations for Demonstrating Surrogacy

**Session I: MRD as a Surrogate Endpoint in Multiple Myeloma**

**Objective:** Discuss the evidence available to support the use of MRD in clinical trials of new treatments for multiple myeloma, explore remaining barriers to the broader use of MRD in multiple myeloma, and identify key next steps for addressing those barriers.

**Questions for Discussion:**

1. What sort of evidence is available to support the validity of MRD as a surrogate endpoint for overall survival (OS) or other endpoint?
2. What analyses have been done to date? What are the strengths and weaknesses of these analyses, and what evidentiary gaps still need to addressed?
3. What other regulatory, scientific, or practical barriers exist for the broader use of MRD in individual drug development programs?

**Session II: MRD as a Surrogate Endpoint in Chronic Lymphocytic Leukemia (CLL)**

**Objective:** Discuss the evidence available to support the use of MRD in clinical trials of new treatments for CLL, explore remaining barriers to the broader use of MRD in CLL, and identify key next steps for addressing those barriers.

**Questions for Discussion:**

1. What sort of evidence is available to support the validity of MRD as a surrogate endpoint for overall survival (OS) or other endpoint?
2. What analyses have been done to date? What are the strengths and weaknesses of these analyses, and what evidentiary gaps still need to addressed?
3. What other regulatory, scientific, or practical barriers exist for the broader use of MRD in individual drug development programs?
Session III: MRD as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL)

Objective: Discuss the evidence available to support the use of MRD in clinical trials of new treatments for ALL, explore remaining barriers to the broader use of MRD in ALL, and identify key next steps for addressing those barriers

Questions for Discussion:

1. What sort of evidence is available to support the validity of MRD as a surrogate endpoint for overall survival (OS) or other endpoint?
2. What analyses have been done to date? What are the strengths and weaknesses of these analyses, and what evidentiary gaps still need to addressed?
3. What other regulatory, scientific, or practical barriers exist for:
   a. The broader use of MRD in individual drug development programs?
   b. The qualification of MRD as a surrogate endpoint?

Session IV: MRD as a Surrogate Endpoint in Acute Myeloid Leukemia (AML)

Objective: Discuss the evidence available to support the use of MRD in clinical trials of new treatments for AML, explore remaining barriers to the broader use of MRD in AML, and identify key next steps for addressing those barriers

Questions for Discussion:

1. What sort of evidence is available to support the validity of MRD as a surrogate endpoint for overall survival (OS) or other endpoint?
2. What analyses have been done to date? What are the strengths and weaknesses of these analyses, and what evidentiary gaps still need to addressed?
3. What other regulatory, scientific, or practical barriers exist for the broader use of MRD in individual drug development programs?

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Kim, C., Prasad, V. (2016).

U.S. Food and Drug Administration. (2013). Public Workshop on Minimal Residual Disease (MRD) as a Surrogate Endpoint in Chronic Lymphocytic Leukemia (CLL).


U.S. Food and Drug Administration. (2013). Public Workshop on Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Myeloid Leukemia (AML).