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Understanding Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a group of conditions characterized by disorders of blood cell production (or hematopoiesis). Normally, immature cells develop within the bone marrow into the three types of blood cells: red cells (which distribute oxygen and eliminate carbon dioxide), white cells (which fight infection), and platelets (which regulate blood clotting). When the cells are fully mature and functioning, the bone marrow releases the blood cells into the circulation. In MDS, a breakdown occurs in this process of hematopoiesis, and blood cells develop improperly. This results in a deficiency in normal blood cell functioning, abnormally low blood cell counts (cytopenias), and an increased percentage of immature (ie, ineffective) blood cells (blasts) in the bone marrow and the blood stream. Statistics released in 1999 indicate there are approximately 13,000 new cases of MDS diagnosed annually, making MDS the most common form of leukemia in the Western Hemisphere ahead of chronic lymphocytic leukemia.

The major problems associated with these disorders are life-threatening complications from bone marrow failure and cytopenias. In addition, some forms of MDS have a high probability of transforming to an acute form of leukemia, with reported transformation rates ranging from 10% to 50%.

Development

Smoking or exposure to certain chemicals such as herbicides and pesticides can increase the risk of MDS, along with exposure to types of chemotherapy that damage the bone marrow. When MDS develops after exposure to any of these agents, it is termed *secondary* or *treatment-related MDS*. Treatment-related MDS accounts for approximately 20% to 30% of cases but is increasing as more patients with cancer are diagnosed and subsequently treated with MDS-associated chemotherapies. When MDS develops in patients with no known exposure to these agents, it is known as *de novo MDS*.

A chromosomal abnormality is detected in approximately 40% to 75% of MDS cases. Specific anomalies include deletions of all or part of chromosome 5 or 7 or additions to chromosome 8. 5q- syndrome is an MDS subtype in which a deletion at chromosome 5q is the sole chromosomal abnormality.

Prevalence

About 14,000 new MDS cases are diagnosed annually in the United States. MDS is generally diagnosed in older adults, with a median age of 65 to 75, but is occasionally

diagnosed in children. Worldwide, the approximate incidence is between 250,000 and 300,000, with an increased incidence in people older than 60. The incidence of MDS is believed to be rising due to a longer average lifespan and an increase in correct diagnoses. MDS occurs slightly more frequently in men than in women, with a male-to-female ratio of 1.3 to 1.

Symptoms

Although symptoms of MDS can vary, patients typically present with anemia-associated symptoms such as weakness and fatigue. Other symptoms may include:

- Frequent infections
- Bruising easily
- Bleeding
- Fever
- Loss of appetite
- Weight loss
- A sense of abdominal fullness

Current Treatments

No single agent has received FDA approval for treating MDS. Currently, the standard of care is supportive care, meaning that treatment options are limited to reducing symptoms rather than treating the underlying causes of the disease. Supportive care options include blood cell transfusions, antibiotics, and the use of certain proteins and growth factors that can help keep blood cell counts within normal range. In general, the use of more aggressive therapy depends upon the patient's individual condition, such as age, ability to function, and disease type. These treatments include chemotherapy, immunosuppressive drugs, and stem cell transplantation. Although these treatments have a greater chance of affecting the disease course, they are also associated with greater morbidity and mortality and are therefore mostly limited to use in clinical trials.

REVIMID™ (CC-5013) for MDS

Developed by Celgene Corporation, **REVIMID™** represents a completely new approach to treating MDS. REVIMID is a member of a new class of novel immunomodulatory drugs, or IMiDs™, which have demonstrated potent anticancer activity. Multiple pivotal Phase III special protocol assessment (SPA) clinical trials for full approval and multiple Phase II trials for accelerated approvals are evaluating REVIMID in the treatment of a broad range of conditions, including; multiple myeloma and other hematological cancers and malignant blood cell disorders such as myelodysplastic syndromes (MDS) and solid tumor cancers. REVIMID has received a Fast Track Designation from the FDA both for the treatment of multiple myeloma and the treatment of MDS.

The IMiDs are believed to affect multiple biological pathways within the cell, which ultimately may be responsible for the clinical activity observed in more than 200 studies worldwide. The IMiD pipeline is covered by a comprehensive intellectual property estate of U.S. and foreign issued patents and pending patent applications including composition-of-matter and use patents.

REVIMID (CC-5013) is not approved by the FDA or any other regulatory agencies as a treatment in multiple myeloma or MDS and is currently being evaluated in clinical trials for efficacy and safety for future regulatory applications.

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