Mylotarg™ (gemtuzumab ozogamicin) – New orphan drug approval

- On September 1, 2017, the FDA announced the approval of Pfizer's Mylotarg (gemtuzumab ozogamicin), for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults, and for the treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.
    - Mylotarg originally received accelerated approval in May 2000 as a stand-alone treatment for older patients with CD33-positive AML who had experienced a relapse.
    - Mylotarg was voluntarily withdrawn from the market after subsequent confirmatory trials failed to verify clinical benefit and demonstrated safety concerns, including a high number of early deaths.
    - Today's approval includes a lower recommended dose, a different schedule in combination with chemotherapy or on its own, and a new patient population.

- AML is a rapidly progressing cancer that forms in the bone marrow and results in an increased number of white blood cells in the bloodstream. The National Cancer Institute estimates that approximately 21,380 people in the U.S. will be diagnosed with AML this year and that 10,590 patients will die of the disease.

- Mylotarg is a targeted therapy that consists of an antibody connected to an anti-tumor agent that is toxic to cells. It is thought to work by taking the anti-tumor agent to the AML cells that express the CD33 antigen, blocking the growth of cancerous cells and causing cell death.

- The safety and efficacy of Mylotarg in combination with chemotherapy were studied in 271 patients with newly diagnosed CD33-positive AML. Patients were randomized to Mylotarg in combination with daunorubicin and cytarabine or daunorubicin and cytarabine without Mylotarg. The trial measured event-free survival (EFS), or how long patients went without certain complications, including failure to respond to treatment, disease relapse, or death.
    - Median EFS for the Mylotarg-treated patients was 17.3 months vs. 9.5 months for the chemotherapy-treated patients (HR = 0.56 [95% CI: 0.42, 0.76]; $p < 0.001$).
    - The safety and efficacy of Mylotarg in combination with daunorubicin and cytarabine have not been established in pediatric patients with newly-diagnosed de novo AML.

- The safety and efficacy of Mylotarg as stand-alone therapy were studied in 2 separate studies. In the first study, 237 patients with newly diagnosed AML were randomized to receive Mylotarg or best supportive care (BSC). The study measured overall survival (OS). In the second study, 57 patients with CD33-positive AML who had experienced one relapse of disease received a single course of Mylotarg. The study measured complete remission (CR).
    - In the first study, median OS was 4.9 months in the Mylotarg arm vs. 3.6 months in BSC arm (HR = 0.69 [95% CI: 0.53, 0.90]; $p = 0.005$).
    - In the second study, 26% (95% CI: 16, 40) of patients achieved CR that lasted a median of 11.6 months.
    - In addition, the safety and efficacy of Mylotarg as a single agent in pediatric patients with relapsed or refractory AML were supported by a single-arm trial in 29 patients. A literature review included an additional 96 patients with ages ranging from 0.2 to 21 years. No differences in efficacy and safety were observed by age.

- Mylotarg carries a boxed warning for hepatotoxicity.

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- Other warnings and precautions of Mylotarg include infusion related reactions (including anaphylaxis), hemorrhage, QT interval prolongation, use in AML with adverse-risk cytogenetics, and embryo-fetal toxicity.

- The most common adverse reactions (> 15%) with Mylotarg use were hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis.

- The recommended dosage of Mylotarg is as follows:

    - The recommended dosage of Mylotarg with combination therapy in adults with newly-diagnosed de novo CD33-positive AML is 1 induction cycle (3 mg/m^2 [up to one 4.5 mg vial] on days 1, 4, and 7 in combination with daunorubicin and cytarabine) and 2 consolidation cycles (3 mg/m^2 [up to one 4.5 mg vial] on day 1 in combination with daunorubicin and cytarabine). Consult the daunorubicin and cytarabine drug labels for dosing recommendations.
    - The recommended dosage of Mylotarg as single-agent therapy in adults with newly-diagnosed CD33-positive AML is 1 cycle of induction (6 mg/m^2 on day 1, and 3 mg/m^2 on day 8) and up to 8 cycles of continuation therapy (2 mg/m^2 on day 1 every 4 weeks).
    - The recommended dosage of Mylotarg as single-agent therapy for the treatment of relapsed or refractory CD33-positive AML is 3 mg/m^2 [up to one 4.5 mg vial] on days 1, 4, and 7.
    - Patients should be premedicated with a corticosteroid, antihistamine, and acetaminophen 1 hour prior to Mylotarg.

- Pfizer plans to launch Mylotarg by the end of next week. Mylotarg will be available as a 4.5 mg lyophilized cake or powder in a single-dose vial for reconstitution and dilution.