Gemtuzumab Ozogamicin (Mylotarg) - Medical Clinical Policy Bulletins | Aetna

Gemtuzumab Ozogamicin (Mylotarg)

Number: 0922

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers gemtuzumab ozogamicin (Mylotarg) medically necessary for the treatment of the following indications:

I. For the treatment of AML when the tumor is CD33-positive as confirmed by testing or analysis to identify the CD33 antigen.

II. Acute promyelocytic leukemia (APL) when any of the following criteria are met:

   A. For treatment in high-risk disease (WBC count > 10,000/mcL);
      or
   B. For relapse.

Aetna considers continued treatment with gemtuzumab ozogamicin medically necessary for members who have not experienced disease progression or an unacceptable toxicity.

Aetna considers gemtuzumab ozogamicin experimental and investigational for the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Acute lymphoblastic leukemia (ALL)
- Granulocytic sarcoma
- Hodgkin lymphoma
- Non-Hodgkin lymphoma (NHL)
- Solid tumors (e.g., breast cancer, glioblastoma, mesothelioma, ovarian cancer, and small cell lung cancer)

See also: CPB 0867 - Clofarabine (Clolar) (/800_899/0867.html), and CPB 0868 - Decitabine (Dacogen) (/800_899/0868.html).

Dosing Recommendations

Pre-medicate with a corticosteroid, anti-histamine, and acetaminophen 1 hour prior to Mylotarg.

For Injection: Mylotarg is available in the form of 4.5-mg as a lyophilized cake or powder in a single-dose vial for reconstitution and dilution.

Newly Diagnosed, De-Novo AML (Combination Regimen)

- Induction: 3 mg/m² (up to one 4.5-mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine
- Consolidation: 3 mg/m² on day 1 (up to one 4.5-mg vial) in combination with daunorubicin and cytarabine.

Newly Diagnosed AML (Single-Agent Regimen)

- Induction: 6 mg/m² on day 1 and 3 mg/m² on day 8
- Continuation: For patients without evidence of disease progression following induction, up to 8 continuation courses of Mylotarg 2 mg/m² on day 1 every 4 weeks.

Relapsed or Refractory AML (Single-Agent Regimen)

- 3 mg/m² on days 1, 4, and 7

Source: Pfizer, 2018.

Background
Acute myeloid leukemia (AML), one of the best studied malignancies, is a rapidly progressing malignancy that forms in the bone marrow (BM) and leads to an increased number of leukocytes in the circulation. The National Cancer Institute estimates that about 21,380 individuals will be diagnosed with AML in 2017; and that 10,590 patients with AML will die of the disease. Stahl and colleagues (2017) stated that while significant advances have been made in the understanding of clinical implications of AML, drug development has not kept pace, as the “7+3” induction regimen remains the standard of care for patients fit for intensive therapy 40 years after its first use. Temporal improvements in overall survival (OS: how long patients survived from the date they started the drug) were mostly confined to younger patients and driven by improvements in supportive care and use of hematopoietic cell transplantation (HCT).

Multiple forms of novel therapy are currently in clinical trials; these novel therapies include improved chemotherapeutic agents, targeted molecular inhibitors, cell cycle regulators, pro-apoptotic agents, epigenetic modifiers, and metabolic therapies. Immunotherapies in the form of vaccines; naked, conjugated and bi-specific monoclonal antibodies (MAbs); cell-based therapy; and immune checkpoint inhibitors are also being evaluated in an effort to replicate the success seen in other malignancies. One of the new therapeutic approaches for newly diagnosed AML as well as relapsed/refractory AML (r/r-AML) is gemtuzumab ozogamicin (GO), a targeted anti-neoplastic agent comprised of a recombinant anti-CD33 MAb linked to calicheamicin.

Acute Myeloid Leukemia (AML)

Li and co-workers (2014) stated that previous studies have showed conflicting results regarding the effectiveness and toxicity of adding GO to induction chemotherapy for newly diagnosed AML. These investigators performed a systematic review and meta-analysis to resolve this controversial issue. Data from 5 randomized phase III clinical trials (3,596 patients: 1,798 GO and 1,798 controls) compared adding GO to induction chemotherapy with induction chemotherapy alone for newly diagnosed AML were meta-analyzed. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and relapse-free survival (RFS), and pooled odds ratios (ORs) and 95% CIs for complete remission (CR) rate, incidences of resistance disease, relapse and toxicity were calculated. Compared with induction chemotherapy alone, adding GO significantly
prolonged OS (HR 0.93, 95 % CI: 0.86 to 1.00, p = 0.05) and RFS (HR 0.87, 95 % CI: 0.79 to 0.95, p = 0.003), decreased the incidences of resistant disease (OR 0.71, 95 % CI: 0.55 to 0.93, p = 0.01) and relapse (OR 0.75, 95 % CI: 0.63 to 0.90, p = 0.002), but had no effect on CR rate (OR 1.15, 95 % CI: 0.91 to 1.46, p = 0.24). Sensitivity analysis yielded similar results. Subgroup analysis identified that cytogenetics might be an influencing factor for the effect of adding GO. In addition, the risks of grade 3 to 4 nausea/vomiting, diarrhea and liver aspartate transaminase (AST) elevation were increased in GO-arm. The authors concluded that adding GO to induction chemotherapy for newly diagnosed AML can significantly prolong OS and RFS, decrease incidences of resistant disease and relapse, but may increase risks of grade 3 to 4 nausea/vomiting, diarrhea and liver AST elevation.

In a phase III clinical trial, Gamis and colleagues (2014) examined if adding GO to standard chemotherapy improved event-free survival (EFS: how long patients went without certain complications, including failure to respond to treatment, disease relapse or death) and OS in children with newly diagnosed AML; secondary objectives were outcomes by risk group and method of intensification. Children, adolescents, and young adults aged 0 to 29 years with newly diagnosed AML were enrolled into the Children’s Oncology Group trial AAML0531 and then were randomly assigned to either standard 5-course chemotherapy alone or to the same chemotherapy with 2 doses of GO (3 mg/m2/dose) administered once in induction course 1 and once in intensification course 2. There were 1,022 evaluable patients enrolled; GO significantly improved EFS (3 years: 53.1 % versus 46.9 %; HR, 0.83; 95 % CI: 0.70 to 0.99; p = 0.04) but not OS (3 years: 69.4 % versus 65.4 %; HR, 0.91; 95 % CI: 0.74 to 1.13; p = 0.39). Although remission was not improved (88 % versus 85 %; p = 0.15), post-hoc analyses found relapse risk (RR) was significantly reduced among GO recipients overall (3 years: 32.8 % versus 41.3 %; HR, 0.73; 95 % CI: 0.58 to 0.91; p = 0.006). Despite an increased post-remission toxic mortality (3 years: 6.6 % versus 4.1 %; HR, 1.69; 95 % CI: 0.93 to 3.08; p = 0.09), disease-free survival (DFS) was better among GO recipients (3 years: 60.6 % versus 54.7 %; HR, 0.82; 9 % CI: 0.67 to 1.02; p = 0.07). The authors concluded that GO added to chemotherapy improved EFS through a reduction in RR for children and adolescents with AML.
Loke and associates (2015) noted that conventional chemotherapy is ineffective in the majority of patients with AML, and GO had been reported to improve outcome in patients with AML. Reports of excess toxicity resulted in the voluntary withdrawal of GO from the U.S. market. These researchers performed a systematic review and meta-analysis that included studies of patients with AML who had entered a randomized control trial (RCT), where 1 arm included anti-CD33 antibody therapy. Fixed effect meta-analysis was used, involving calculation of observed minus expected number of events, and variance for each end-point in each trial, with the overall treatment effect expressed as Peto's OR with 95% CI. Meta-analysis of 11 RCTs with 13 randomizations involving GO was undertaken. Although GO increased induction deaths (p = 0.02), it led to a reduction in resistant disease (p = 0.0009); hence, there was no improvement in CR. While GO improved RFS (HR = 0.90, 95% CI: 0.84 to 0.98, p = 0.01), there was no overall benefit of GO in OS (HR = 0.96, 95% CI: 0.90 to 1.02, p = 0.2). Gemtuzumab ozogamicin improved OS in patients with favorable cytogenetics, with no evidence of benefit in patients with intermediate or adverse cytogenetics (test for heterogeneity between subtotals p = 0.01). The authors concluded that GO had a potent clinically detectable anti-leukemic effect. They stated that further clinical trials are needed to examine its optimum delivery and identification of patient populations who may benefit.

Pollard and colleagues (2016) stated that CD33 is variably expressed on AML blasts and is targeted by GO, which had shown benefit in both adult and pediatric AML trials, yet limited data exist about whether GO response correlates with CD33 expression level. In a phase III clinical trial, CD33 expression levels were prospectively quantified by multi-dimensional flow cytometry in 825 patients enrolled in the Children's Oncology Group AAML0531 and correlated with response to GO. Patients with low CD33 expression (lowest quartile of expression [Q1]) had no benefit with the addition of GO to conventional chemotherapy (RR: GO 36% versus No-GO 34%, p = 0.731; EFS: GO 53% versus No-GO 58%, p = 0.456). However, patients with higher CD33 expression (Q2 to Q4) had significantly reduced RR (GO 32% versus No-GO 49%, p < 0.001) and improved EFS (GO 53% versus No-GO 41%, p = 0.005). This differential effect was observed in all risk groups. Specifically, low-risk (LR), intermediate-risk (IR), and high-risk (HR) patients with low CD33 expression had similar outcomes regardless of GO exposure,
whereas the addition of GO to conventional chemotherapy resulted in a significant decrease in RR and improvement in DFS for patients with higher CD33 expression (LR RR, GO 13 % versus No-GO 35 %, p = 0.001; LR DFS, GO 79 % versus No-GO 59 %, p = 0.007; IR RR, GO 44 % versus No-GO 57 %, p = 0.044; IR DFS, GO 51 % versus No-GO 40 %, p = 0.078; HR RR, GO 40 % versus No-GO 73 %, p = 0.016; HR DFS, GO 47 % versus No-GO 28 %, p = 0.135). The authors demonstrated that GO lacked clinical benefit in patients with low CD33 expression; but significantly reduced RR and improved EFS in patients with high CD33 expression suggesting a role for CD33-targeted therapeutics in subsets of pediatric AML.

Hutter-Kronke et al (2016) noted that outcome of patients with primary refractory AML remains unsatisfactory. These investigators conducted a prospective phase II clinical trial with GO (3 mg/m(2) intravenously on day 1), all-trans retinoic acid (45 mg/m(2) orally on days 4 to 6 and 15 mg/m(2) orally on days 7 to 28), high-dose cytarabine (3 g/m(2)/12 hours intravenously on days 1 to 3) and mitoxantrone (12 mg/m(2) intravenously on days 2 to 3) in 93 patients aged 18 to 60 years refractory to 1 cycle of induction therapy. Primary end-point was response to therapy; secondary end-points included evaluation of toxicities, in particular, rate of hepatic veno-occlusive disease (VOD) (also known as sinusoidal obstruction syndrome) after allogeneic HCT (allo-HCT). Complete remission or CR with incomplete blood count recovery (Cri) was achieved in 47 (51 %) and partial remission (PR) in 10 (11 %) patients resulting in an overall response rate (ORR) of 61.5 %; 33 (35.5 %) patients had refractory disease and 3 patients (3 %) died; allo-HCT was performed in 71 (76 %) patients; 6 of the 71 (8.5 %) patients developed moderate or severe hepatic VOD after allo-HCT; 4-year OS rate was 32 % (95 % CI: 24 % to 43 %). Patients responding to salvage therapy and undergoing allo-HCT (n = 51) had a 4-year survival rate of 49 % (95 % CI: 37 % to 64 %). Patients with fms-like tyrosine kinase internal tandem duplication-positive AML had a poor outcome despite transplantation. The authors concluded that the described regimen was an effective and tolerable salvage therapy for patients who are primary refractory to 1 cycle of conventional intensive induction therapy.
Burnett and colleagues (2016) stated that a recent meta-analysis of randomized trials in adults assessing GO combined with standard chemotherapy in AML showed a significant survival benefit in patients without an adverse karyotype. It is unclear whether the optimal dose should be 3 mg/m\(^2\) or 6 mg/m\(^2\). In this study, these researchers randomized 788 patients to a single-dose of GO 3 mg/m\(^2\) or 6 mg/m\(^2\) with the 1st course of induction therapy. They found that the rate of CR was higher with 3 mg/m\(^2\) [82 % versus 76 %; OR 1.46 (1.04 to 2.06); \(p = 0.03\)], but this was balanced by a higher rate of Cri in the 6 mg/m\(^2\) treatment (10 % versus 7 %) resulting in similar ORR [89 % versus 86 %; HR 1.34 (0.88 to 2.04); \(p = 0.17\)]. There was no overall difference in relapse or survival at 4 years between the arms: 46 % versus 54 %; HR 1.17 (0.94 to 1.45), \(p = 0.5\), and 50 % versus 47 %; HR 1.10 (0.90 to 1.34), \(p = 0.3\), respectively. The 30- and 60-day mortality was significantly higher in the 6 mg/m\(^2\) recipients: 7 % versus 3 %; HR 2.07 (1.11 to 3.87), \(p = 0.02\), and 9 % versus 5 %; HR 1.99 (1.17 to 3.39), \(p = 0.01\), respectively, which in addition was associated with a higher rate of VOD (5.6 % versus 0.5 %; \(p < 0.0001\)). The authors concluded that there was no advantage in using a single-dose of 6 mg/m\(^2\) of GO in combination with induction chemotherapy when compared with a 3 mg/m\(^2\) dose, with respect to response, DFS and OS, either overall, or in any disease subgroup.

In a phase III clinical trial, Amadori and associates (2016) compared single-agent GO with best supportive care (BSC) including hydroxyurea as 1st-line therapy in older patients with AML unsuitable for intensive chemotherapy. Patients at least 61 years old were randomized (1:1) to receive either a single induction course of GO (6 mg/m\(^2\) on day 1 and 3 mg/m\(^2\) on day 8) or BSC. Patients who did not progress after GO induction could receive up to 8 monthly infusions of GO at 2 mg/m\(^2\). Randomization was stratified by age, World Health Organization (WHO) performance score, CD33 expression status, and center. The primary end-point was OS by intention-to-treat analysis. A total of 237 patients were randomly assigned (118 to GO and 119 to BSC). The median OS was 4.9 months (95 % CI: 4.2 to 6.8 months) in the GO group and 3.6 months (95 % CI: 2.6 to 4.2 months) in the BSC group (HR, 0.69; 95 % CI: 0.53 to 0.90; \(p = 0.005\)); the 1-year OS rate was 24.3 % with GO and 9.7 % with BSC. The OS benefit with GO was consistent across most subgroups, and was especially apparent in patients with high CD33
expression status, in those with favorable/intermediate cytogenetic risk profile, and in women. Overall, CR + CRi occurred in 30 of 111 (27%) GO recipients. The rates of serious adverse events (AEs) were similar in the 2 groups, and no excess mortality from AEs was observed with GO. The authors concluded that 1st-line monotherapy with low-dose GO, as compared with BSC, significantly improved OS in older patients with AML who were ineligible for intensive chemotherapy; no unexpected AEs were identified and toxicity was manageable.

Lamba and co-workers (2017) stated that GO is a re-emerging therapy for AML. In a phase III clinical trial, these researchers determined the impact of CD33 splicing polymorphism in patients with AML treated with GO-containing chemotherapy. CD33 splicing single nucleotide polymorphism (SNP) was evaluated in newly diagnosed patients with AML randomly assigned to receive standard 5-course chemotherapy alone (No-GO arm, n = 408) or chemotherapy with the addition of 2 doses of GO -- once during induction and once during intensification (GO arm, n = 408) -- as per the Children's Oncology Group AAML0531 trial. The rs12459419 genotype was CC in 415 patients (51%), CT in 316 patients (39%), and TT in 85 patients (10%), with a minor allele frequency of 30%. The T allele was significantly associated with higher levels of D2-CD33 transcript (p < 1.0E-6) and with lower diagnostic leukemic cell surface CD33 intensity (p < 1.0E-6). Patients with the CC genotype had significantly lower RR in the GO arm than in the No-GO arm (26% versus 49%; p < 0.001). However, in patients with the CT or TT genotype, exposure to GO did not influence RR (39% versus 40%; p = 0.85); DFS was higher in patients with the CC genotype in the GO arm than in the No-GO arm (65% versus 46%, respectively; p = 0.004), but this benefit of GO addition was not observed in patients with the CT or TT genotype. The authors concluded that these findings suggested that patients with the CC genotype for rs12459419 had a substantial response to GO, making this a potential biomarker for the selection of patients with a likelihood of significant response to GO.

On September 1, 2017, the Food and Drug Administration (FDA) approved Mylotarg (gemtuzumab ozogamicin) for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33-positive AML). The FDA also approved Mylotarg for the treatment of patients aged 2 years and older with CD33-positive AML who have
Gemtuzumab ozogamicin (Mylotarg) was studied in a trial of 271 patients with newly diagnosed CD33-positive AML who were randomized to receive GO in combination with daunorubicin and cytarabine or to receive daunorubicin and cytarabine without GO. The trial measured EFS from the date they started the trial. Patients who received GO in combination with chemotherapy went longer without complications than those who received chemotherapy alone (median EFS of 17.3 months versus 9.5 months). The safety and efficacy of GO as a stand-alone treatment were studied in 2 separate trials. The 1st trial included 237 patients with newly diagnosed AML who could not tolerate or chose not to receive intensive chemotherapy. Patients were randomized to receive treatment with GO or BSC. The trial measured OS. Patients who received GO survived longer than those who received only BSC (median OS of 4.9 months versus 3.6 months). The 2nd trial was a single-arm study that included 57 patients with CD33-positive AML who had experienced 1 relapse of disease. Patients received a single course of GO. The trial measured how many patients achieved a CR. Following treatment with GO, 26% of patients achieved a CR that lasted a median of 11.6 months. Common AEs associated with the use of GO include fever, nausea, infection, vomiting, bleeding, thrombocytopenia, stomatitis, constipation, rash, headache, elevated liver function tests, and neutropenia. Severe AEs of GO include low blood counts, infections, liver damage, hepatic VOD, infusion-related reactions, and hemorrhage.

Women who are pregnant or breast-feeding should not take GO because it may cause harm to a developing fetus or a newborn baby. Patients with hypersensitivity to GO or any component of its formulation should not use GO. The prescribing information for GO includes a boxed warning that severe or fatal hepatotoxicity, including hepatic VOD occurred in some patients who took GO.

Gemtuzumab ozogamicin is also being studied for the treatment of various malignancies including hematologic diseases, granulocytic sarcoma, and solid tumors; however, its effectiveness for these indications has not been established.

Acute Lymphoblastic Leukemia (ALL)
Hoelzer (2011) noted that a major breakthrough in the treatment of acute lymphoblastic leukemia (ALL) was the availability of targeted therapies targeting either specific transcripts, such as bcr-abl fusion protein by tyrosine kinase inhibitors, or specific antigens by MAbs. ALL blast cells express a variety of specific antigens (e.g., CD19, CD20, CD22, CD33, and CD52) that serve as targets for MAbs. To-date, the most data are available for anti-CD20 (rituximab), which has been combined with chemotherapy for the treatment of mature B-ALL/Burkitt lymphoma. Studies with rituximab have also been completed in B-precursor ALL. Another antigen, CD19, is of great interest due to a very high rate of expression in ALL. It can be targeted by a bi-specific MAb, blinatumomab, directed against CD19 and CD3. Smaller studies or case reports were also available for the anti-CD52 (alemtuzumab), anti-CD22 (epratuzumab), and anti-CD33 (GO) MAbs. Available data demonstrated that MAb therapy in ALL is a highly promising approach. However, several details for an optimal therapeutic approach, such as the required level of antigen expression, timing, schedule, dosage, and stage of disease, still need to be defined.

Acute Promyelocytic Leukemia (APL)

Norsworthy and Altman (2016) stated that despite major advances in the treatment of acute promyelocytic leukemia (APL), high-risk APL still poses unique challenges. These investigators outlined current evidence for evaluation and management of high-risk APL and discussed areas of ongoing and future investigation. With the changing treatment paradigm in APL and increasing use of arsenic trioxide (ATO), reports have questioned the relevance of classic prognostic factors. Despite advancements in therapy, early death remains a primary reason for treatment failure. A randomized, phase III clinical trial demonstrated that all-trans retinoic acid + ATO is at least non-inferior and may be superior to all-trans retinoic acid + chemotherapy in LR-APL/IR-APL. One phase III and multiple phase II clinical trials have suggested a benefit of adding ATO to therapy of high-risk patients. Attempts at minimizing chemotherapy in high-risk disease have proven feasible with the use of GO, but it is unlikely that cytotoxic chemotherapy will be completely eliminated in this patient population. The authors concluded that
treatment of high-risk APL has evolved significantly over the past 10 years; however, there are as yet unresolved questions, including how to minimize early deaths and optimal therapy in an ATO era.

Granulocytic Sarcoma

Gossai and colleagues (2016) stated that granulocytic sarcoma (GS) is a rare manifestation of myeloid proliferation, characterized by formation of a mass comprised of immature cells of myeloid origin. Orbital GS is rarer still, with only a small fraction of GS patients having orbital involvement. Given the rarity of orbital GS, no unified therapy plan has been identified, as large prospective trials are not feasible, but it is widely accepted that patients with GS ought to be treated with systemic intensive chemotherapy consistent with standard of care regimens for AML or chronic myelogenous leukemia (CML). Patients with GS associated with CML should receive CML-specific therapy. When conventional and traditional cytotoxic GS/AML chemotherapy regimens are insufficient, patients often require a combination of novel therapeutics, HCT, and radiation. Much of the recent advancement in AML therapy, as well as in AML translational research, has focused on targeting molecular facets of the disease and enabling more specificity with treatment. The aim of treating patients for whom conventional treatment was unsuccessful with personalized therapy has not yet been realized, but many of the novel therapeutics reviewed have demonstrated promise and are cause for optimism. The authors noted that in their center, when a GS/AML patient is refractory to front-line therapy, they rely on novel chemotherapy therapeutic options; and GO was one of the keywords in this study.

Hodgkin Lymphoma (HL)

Bander and colleagues (2012) noted that antibody-drug conjugates (ADCs) combine cytotoxic chemotherapy and antibody specificity. There are 4 components of ADC technology: (i) the cancer, or target, antigen; (ii) the antibody to that target; (iii) the linker that connects the drug to the antibody; and (iv) the drug itself. The antibody directs the cytotoxic agent to the tumor cell, thereby diminishing the side effect profile of the cytotoxic agent and enabling delivery of a more potent therapeutic because of the ability to control the target and the side effects. Antibody-drug conjugates technology has markedly improved in the past few
years. In early ADCs, the linkers were too labile, which led to the release of free drug in the circulation and consequent off-target toxicity. In the current generation of ADCs, the linkers are more stable, and the cytotoxic agents are significantly more potent. Antibody-drug conjugates have been developed against a variety of antigens and receptors, including CD19, CD22, and CD30, and have been linked to multiple different cytotoxic agents, including calicheamicin and maytansinoid derivatives. The ADC brentuximab vedotin was recently approved by the FDA for the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (auto-SCT) or at least 2 prior multi-agent chemotherapy regimens, and the treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least 1 prior multi-agent chemotherapy regimen. Other ADCs in clinical trials for hematologic disorders include inotuzumab ozogamicin, SAR3419, and GO.

Non-Hodgkin Lymphoma (NHL)

Mehta and Forero-Torres (2015) noted that rituximab (a MAb against CD20) was the first MAb approved by the FDA for treatment of B cell non-Hodgkin lymphoma (B-NHL). Conjugating toxins to MAb was a technical challenge; however, with improvements in linker technology, immuno-conjugates were constructed and revolutionized cancer treatment; GO was the first ADC approved by the FDA. Because of the success of brentuximab vedotin and ado-trastuzumab emtansine in treating HL and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, respectively, newer ADCs are being investigated. Brentuximab vedotin was approved for both HL and anaplastic large cell lymphoma. Newer ADCs, such as polatuzumab vedotin (targeting CD79b), pinatuzumab vedotin (targeting CD22), inotuzumab ozogamicin (targeting CD19), SAR3419 (targeting CD19), IMGN529 (targeting CD37), and SGN-CD19A (targeting CD19), have shown promising pre-clinical and early clinical activity. These findings will change the landscape of B-NHL treatment away from CHOP-based chemotherapies.

Solid Tumors
Lambert and Morris (2017) noted that attaching a cytotoxic "payload" to an antibody to form an ADC provides a mechanism for selective delivery of the cytotoxic agent to cancer cells via the specific binding of the antibody to cancer-selective cell surface molecules. The first ADC to receive marketing authorization was GO, which comprises an anti-CD33 antibody conjugated to a highly potent DNA-targeting antibiotic, calicheamicin, approved in 2000 for treating AML. It was withdrawn from the US market in 2010 following an unsuccessful confirmatory trial. The development of 2 classes of highly potent microtubule-disrupting agents, maytansinoids and auristatins, as payloads for ADCs resulted in approval of brentuximab vedotin in 2011 for treating HL and ALCL, and approval of ado-trastuzumab emtansine in 2013 for treating HER2-positive breast cancer. Their success stimulated much research into the ADC approach, with more than 60 ADCs currently in clinical evaluation, mostly targeting solid tumors; 5 ADCs have advanced into pivotal clinical trials for treating various solid tumors including breast cancer, glioblastoma, mesothelioma, glioblastoma, ovarian cancer, and small cell lung cancer.

NCCN Recommendations

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium (2019) for gemtuzumab ozogamicin (Mylotarg) include the following recommendations:

**Acute Myeloid Leukemia (AML)**

For treatment induction for patients with CD33-positive AML

- in patients age <60 years in combination with standard-dose cytarabine and daunorubicin (the addition of gemtuzumab ozogamicin may benefit patients with core binding factor (CBF) abnormalities)
- in patients age ≥60 years in combination with standard-dose cytarabine and daunorubicin in candidates for intensive remission induction therapy with de novo AML without unfavorable cytogenetics/molecular markers/no antecedent hematologic disorder/no therapy-related AML
- in patients age ≥60 years as a single agent without actionable mutations when not a candidate for intensive remission induction
therapy or declines intensive therapy.

For post-remission therapy for patients with CD33-positive AML

- in combination with intermediate-dose cytarabine and daunorubicin for patients age <60 years with core binding factor (CBF) cytogenetic translocations without KIT mutation or favorable-risk molecular abnormalities, or intermediate-risk cytogenetics and/or molecular abnormalities
- in combination with intermediate-dose cytarabine and daunorubicin for patients age ≥60 years with complete response to previous intensive therapy
- as a single agent following response to previous lower intensity therapy with the same regimen.

For relapsed/refractory disease for patients with CD33-positive AML

- as a component of repeating the initial successful induction regimen if late relapse (≥12 months)
- as a single agent.

*Acute Myeloid Leukemia (AML) - Acute Promyelocytic Leukemia*

For consolidation therapy in high-risk disease (white blood cell count >10,000/mcL) in patients with cardiac issues (low ejection fraction [EF] or prolonged QTc)

- in combination with tretinoin (ATRA) if arsenic trioxide was discontinued due to toxicity (if low ejection fraction)
- in combination with arsenic trioxide if ATRA was discontinued due to toxicity (if low ejection fraction)
- in combination with ATRA (if prolonged QTc)

For consolidation therapy in high-risk disease (white blood cell count >10,000/mcL) in patients with no cardiac issues

- in combination with tretinoin (ATRA) if arsenic trioxide was discontinued due to toxicity (preferred regimen)
- in combination with arsenic trioxide if ATRA was discontinued due to toxicity (preferred regimen)

**Therapy for first relapse (morphologic or molecular)**

- in combination with arsenic trioxide, with or without tretinoin (ATRA), in patients with no prior exposure to arsenic trioxide or early relapse (<6 months) after ATRA + anthracycline-containing regimen
- in combination with arsenic trioxide, with or without ATRA, in patients with late relapse (≥6 months) after arsenic trioxide-containing regimen

For treatment induction in high-risk disease (white blood cell count >10,000/µL) in patients with no cardiac issues in combination with tretinoin (ATRA) and arsenic trioxide (preferred regimen)

For treatment induction in high-risk disease (white blood cell count >10,000/µL) in patients with cardiac issues

- in combination with tretinoin (ATRA) and arsenic trioxide (if low ejection fraction)
- in combination with ATRA (if prolonged QTc).

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "*":*

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<th>Code Description</th>
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ICD-10 codes covered if selection criteria are met:

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<tr>
<td>C92.A2</td>
<td>Acute myeloid leukemia with multilineage dysplasia, in relapse [CD33-positive AML]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C34.90</td>
<td>Malignant neoplasm of unspecified part of bronchus or lung [small cell lung cancer]</td>
</tr>
<tr>
<td>C34.92</td>
<td></td>
</tr>
<tr>
<td>C45.0</td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>C45.9</td>
<td></td>
</tr>
<tr>
<td>C50.011</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>C50.929</td>
<td></td>
</tr>
<tr>
<td>C56.1</td>
<td>Malignant neoplasm of ovary</td>
</tr>
<tr>
<td>C56.9</td>
<td></td>
</tr>
<tr>
<td>C71.9</td>
<td>Malignant neoplasm of brain, unspecified [Glioblastoma]</td>
</tr>
<tr>
<td>C85.80</td>
<td>Non-hodgkin lymphoma</td>
</tr>
<tr>
<td>C85.99</td>
<td></td>
</tr>
<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia [ALL]</td>
</tr>
<tr>
<td>C91.02</td>
<td></td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


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Amendment to
Aetna Clinical Policy Bulletin Number: 0922
Gemtuzumab Ozogamicin (Mylotarg)

There are no amendments for Medicaid.