Reference number(s)
4458-A

Standard Medicare Part B Management Leukine

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Leukine	sargramostim

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Acute Myeloid Leukemia Following Induction Chemotherapy

Leukine is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).

Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

Leukine is indicated in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

Leukine is indicated for acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).

Allogeneic Bone Marrow Transplantation (BMT)

Leukine is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic BMT from human leukocyte antigens (HLA)-matched related donors.

Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

Leukine is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.

Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

Leukine is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

Compendial Uses

- Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
- Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
- Acute myeloid leukemia
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Neuroblastoma
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Crohn's disease
- Malignant melanoma
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination, response enhancement
- Metastatic renal cell carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Primary Prophylaxis of Febrile Neutropenia

Documentation of the member's diagnosis and chemotherapeutic regimen.

Reference number(s)
4458-A

Coverage Criteria

Neutropenia in Cancer Patients Receiving Myelosuppressive Chemotherapy

Authorization of 6 months may be granted for prevention or treatment of febrile neutropenia when both of the following criteria are met:

- The member will not receive chemotherapy at the same time as they receive radiation therapy.
- One of the following criteria is met:
    - The requested medication will be used for primary prophylaxis or secondary prophylaxis of febrile neutropenia in members with solid tumors or non-myeloid malignancies.
    - The requested medication will be used for treatment of high-risk febrile neutropenia (FN) in members who have any of the following prognostic factors that are predictive of clinical deterioration:
        - Age greater than 65 years
        - Being hospitalized at the time of the development of fever
        - Sepsis syndrome
        - Invasive fungal infection
        - Pneumonia or other clinically documented infection
        - Prolonged (neutropenia expected to last greater than 10 days) or profound (absolute neutrophil count less than 0.1 x 10^9/L) neutropenia
        - Prior episodes of febrile neutropenia

Neuroblastoma

Authorization of 6 months may be granted for treatment of high-risk neuroblastoma when used with one of the following:

- Dinutuximab (Unituxin) and isotretinoin (13-cis-retinoic acid [RA])
- Temozolomide, irinotecan, and dinutuximab (Unituxin)
- Naxitamab-gqgk (Danyelza)

Malignant Melanoma

Authorization of 6 months may be granted for the treatment of malignant melanoma when used in either of the following settings:

- For metastatic melanoma in combination with temozolomide, interferon-alfa 2b, and interleukin-2.
- As adjuvant therapy in stage III or stage IV disease

Other Indications

Authorization of 6 months may be granted for members with any of the following indications:

- Myelodysplastic syndrome (anemia or neutropenia)
- Acute myeloid leukemia

- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Hematopoietic Syndrome of Acute Radiation Syndrome:
  Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
- Moderately to severely active Crohn's disease
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination response enhancement
- Renal cell carcinoma with pulmonary metastases when used with Interleukin-2 therapy

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted for the treatment of renal cell carcinoma when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
  - No evidence of unacceptable toxicity while on current regimen
  - No evidence of disease progression while on the current regimen.

Authorization of 6 months may be granted for the treatment of pulmonary alveolar proteinosis when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

For all other diagnoses, all members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Leukine.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs

    - Clinical Pharmacology
- The prescribing information for Danyelza.
- NCCN Guideline: Hematopoietic growth factors
- NCCN Guideline: Acute myeloid leukemia
- NCCN Guideline: Neuroblastoma
- Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update.
- 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leukine are covered in addition to the following:

- Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
- Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
- Acute myeloid leukemia
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Neuroblastoma
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Crohn's disease
- Malignant melanoma
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination, response enhancement
- Metastatic renal cell carcinoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Leukine prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies can be found in the National Comprehensive Cancer Network's guideline for Hematopoietic Growth Factors. The NCCN Guideline for Hematopoietic Growth Factors supports the use of Leukine for treatment of chemotherapy-induced febrile neutropenia in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.

Support for using Leukine to treat neutropenia and anemia in patients with MDS can be found in several studies listed in the American Hospital Formulary System Drug Information reference. Leukine has been used in an effort to increase leukocyte counts in some adults with myelodysplastic syndrome (MDS) classified as refractory anemia (RA), refractory anemia with excess blasts (RAEB), or refractory anemia with excess blasts in transformation (RAEB-T). While the drug has shown some promise for this use, further study is needed to evaluate the benefits and risks of biosynthetic GM-CSF therapy in patients with MDS, pending accumulation of such data, this use generally should be limited to protocol

conditions. MDS is a heterogeneous group of disorders and several factors (e.g., biologic characteristics of the leukemic clone, presence of an abnormal karyotype, or high initial leukemia burden) may result in considerable variation in response to sargramostim therapy. Use of sargramostim therapy in patients with MDS generally results in an increase in the absolute number of granulocytes and monocytes in most patients and an increase in the absolute number of eosinophils and lymphocytes in many patients. Although an increase in platelets and/or reticulocytes is evident in a few patients with MDS receiving sargramostim, platelet and reticulocyte counts are unaffected in most patients and the need for red blood cell transfusions generally is unchanged during therapy with the drug. Prolonged maintenance therapy with sargramostim appears necessary in patients with MDS since leukocyte counts return to pretreatment levels within 2–10 days after sargramostim is discontinued.Whether use of sargramostim in patients with MDS will alter (either increase or decrease) the rate of progression to AML or affect the usually fatal outcome of the disease is unclear and requires further study. The rate of progression to AML in untreated patients with MDS is approximately 10–20%, 40–50%, or 60–75% in those with RA, RAEB, or RAEB-T, respectively. There is concern, but no clear evidence indicated to date, that use of biosynthetic GM-CSFs may stimulate progression to AML in patients with MDS since in vitro evidence indicates that the drugs can stimulate the growth of myeloid leukemic blast cells and because an increase in the percentage of leukemic blasts in both bone marrow and peripheral blood has occurred in some patients with MDS receiving sargramostim. Although filgrastim (a biosynthetic G-CSF) also has been used in the treatment of MDS, the relative efficacy of these two hematologic growth factors has not been evaluated to date in controlled studies.

Support for using Leukine to treat acute myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for acute myeloid leukemia. The NCCN Guideline states there is no evidence for whether growth factors have a positive or negative impact on long-term outcome if used during consolidation. Growth factors may be considered as part of supportive care for postremission therapy. Growth factors are not routinely recommended in postremission therapy, except in life-threatening infections or when signs and symptoms of sepsis are present, and the leukemia is believed to be in remission.

Support for using Leukine to treat non-chemotherapy drug induced agranulocytosis can be found in a study by Rospond, Glowacki and Mailliard. Leukine has been used effectively in several patients to hasten recovery from sulfasalazine-associated agranulocytosis. A case report by Bjorkhom and colleagues found biosynthetic GM-CSFs can be used to treat methimazole-associated agranulocytosis in a patient with hyperthyroidism.

Support for using Leukine to treat aplastic anemia can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used with some success in an effort to increase leukocyte counts in a limited number of adults and adolescents 15 years of age or older with moderate to severe aplastic anemia. Use of biosynthetic GM-CSFs such as Leukine in these patients resulted in an increase in ANCs that was sustained throughout the period of treatment and a transient increase in absolute eosinophil counts; most patients also had an increase in monocyte and lymphocyte counts. Erythrocyte and platelet counts and transfusion requirements generally were unaffected, although a few patients had increases in hemoglobin concentrations and/or platelet counts. Further study is needed to evaluate more fully use of sargramostim in aplastic anemia and to determine the optimum dosage and long-term safety and efficacy of the drug in these patients; pending accumulation of such data, this use generally should be limited to protocol conditions.

Support for using Leukine to treat neutropenia related to HIV/AIDS can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used in patients with human immunodeficiency virus (HIV) infection in an effort to correct or minimize HIV-associated neutropenia and/or for the treatment of drug-induced neutropenia (e.g., neutropenia associated with use of zidovudine, interferon alfa, and/or cytotoxic chemotherapy) in HIV-infected patients. When used in patients with HIV infection, biosynthetic GM-CSFs effectively increase the number of neutrophils, monocytes, and eosinophils in most patients; however, the drugs appear

to have no consistent effect on the absolute number of lymphocytes nor on the ratio of helper/inducer ($CD4^+$, $T4^+$) to suppressor/cytotoxic ($CD8^+$, $T8^+$) T cells.

Support for using Leukine for stem cell transplantation-related indications can be found in the American Society of Clinical Oncology clinical practice guideline. The ASCO guideline supports using Leukine for mobilization and after transplantation of autologous PBPC and after autologous or allogenic bone marrow transplant. Leukine should be started on the day of the bone marrow transplant and continue until the absolute neutrophil count is greater than 1.5x10(9)/L for three consecutive days. Leukine should be discontinued early or the dose of Leukine should be reduced by 50% if the absolute neutrophil count increases to greater than 20x10(9)/L.

Support for using Leukine in combination with Danyelza to treat neuroblastoma can be found in the prescribing information for Danyelza. Danyelza is indicated, in combination with GM-CSF, for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

Support for using Leukine in combination with dinutuximab (Unituxin) and isotretinoin (13-cis-retinoic acid [RA]) or Leukine in combination with temozolomide, irinotecan, and dinutuximab (Unituxin) to treat high-risk neuroblastoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Leukine to treat severe chronic neutropenia (congenital, cyclic, or idiopathic) can be found in several studies listed in the American Hospital Formulary Service Drug Information reference. Sargramostim has been used with variable success in an effort to increase neutrophil counts in patients with various primary neutropenias, including congenital neutropenia, acquired idiopathic neutropenia, and glycogen storage disease type Ib. In addition, another biosynthetic GM-CSF, molgramostim, has been used with some success in patients with congenital neutropenia, cyclic neutropenia, acquired idiopathic neutropenia, or autoimmune neutropenia. While biosynthetic GM-CSFs may ameliorate the underlying neutropenia in certain patients with these conditions, this effect is unpredictable and not all patients with primary neutropenias respond to the drugs. Filgrastim (a biosynthetic G-CSF) has effectively increased neutrophil counts in some patients with severe congenital neutropenia, chronic idiopathic neutropenia, or cyclic neutropenia who did not respond to sargramostim therapy. In addition, it has been suggested that filgrastim may be more effective than sargramostim or other biosynthetic GM-CSFs in the treatment of primary neutropenia since filgrastim therapy results in more consistent increases in the neutrophil count and does not cause eosinophilia. In a study in children 1–19 years of age with severe congenital neutropenia (Kostmann syndrome), sargramostim therapy resulted in an increase in the absolute granulocyte count in all patients. However, an increase in the ANC occurred in only one patient; in most patients, the increase in granulocytes during sargramostim therapy resulted from an increase in eosinophils or monocytes rather than neutrophils. When sargramostim was used in a few patients with glycogen storage disease type Ib, neutrophil counts increased during therapy with the drug and there was a decrease in inflammatory bowel symptoms. Use of sargramostim in a patient with idiopathic neutropenia also resulted in an increase in the neutrophil count.

Support for using Leukine to treat Crohn's disease can be found in a study by Korzenik and colleagues. Korzenik et al conducted a multicenter, randomized, placebo-controlled trial of 124 patients with Crohn's disease that concluded Leukine improved clinical response and remission when compared to placebo; however, the primary study endpoint was not met. Patients with moderate to severe active Crohn disease (defined as a score of 220 to 475 on the Crohn Disease Activity Index (CDAI)) and no prior history of sargramostim or filgrastim use were eligible for enrollment. Thirty-five percent of patients who were on stable doses of antibiotics and/or aminosalicylates for at least 4 weeks were included

in the study; however, use of azathioprine, mercaptopurine, methotrexate, or oral or rectal glucocorticoids within 4 weeks or antitumor necrosis factor therapy within 12 weeks of study treatment was not permitted. Patients were randomized (2:1) to receive either sargramostim 6 micrograms/kilogram (mcg/kg) (n=81; median age, 36 years (yr); median CDAI score, 300) or placebo (n=43; median age, 41 yr; median CDAI score, 300) subcutaneously once daily for 56 days. Most patients in this study had previously received glucocorticoids (90%) and/or immunosuppressive medications (69%). At day 57, the primary endpoint of a clinical response defined as a CDAI score decrease of at least 70 points from baseline was not significantly different between the 2 study arms (sargramostim arm, 54%; placebo arm, 44%; p=0.28). However, significantly more patients treated with sargramostim compared to placebo achieved the predefined secondary endpoints of clinical response defined as a CDAI score decrease of at least 100 points from baseline (48% versus (vs) 26%; p=0.01), remission at day 57 (defined as a CDAI score of 150 or less) (40% vs 19%; p=0.01), and improved quality of life (defined as an increase in the Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline) (28 vs 16 points; p=0.04) at day 57. Additionally, the median CDAI score was significantly lower at day 57 in the sargramostim-treated patients than in the placebo-treated patients (184 vs 240; p=0.02). At 30 days following treatment, evaluable patients who received sargramostim (n=53) had higher clinical response and remission rates compared to patients who received placebo (n=30) (CDAI score decrease of at least 70, 48% vs 28%; p=0.03; CDAI score decrease of at least 100, 42% vs 21%; p=0.02; remission, 33% vs 14%, p=0.02). Adverse events which occurred significantly (p less than 0.001) more often in the sargramostim arm compared to the placebo arm were injection-site reactions (90% vs 12%) and bone pain (37% vs 7%). Serious adverse events possibly related to sargramostim therapy occurred in 3 patients and included migraine; anorexia, weakness and lethargy; and right-sided weakness consistent with a demyelinating event.

Support for using Leukine to treat malignant melanoma can be found in a study by Spitler et al. In an open-label, multicenter, phase II trial, granulocyte-macrophage colony-stimulating factor (GM-CSF) may be a useful adjuvant therapy to prolong survival in patients with stage III or IV malignant melanoma. Patients who were clinically disease-free as a result of surgical resection of nodal or metastatic disease (n=48) were administered multiple 28-day cycles of subcutaneous GM-CSF 125 micrograms/square meter once daily for 14 days followed by 14 days of rest. Median treatment duration was 11.5 cycles (range 2 to 49). The response of these patients was compared to historical controls matched for age, sex, and the number of positive nodes in stage III patients, and the presence of visceral or nonvisceral metastases and site of metastasis in stage IV patients. Overall median survival was significantly longer in patients who received GM-CSF as compared to the historical controls (37.5 months and 12.2 months; p less than 0.001) with 1-year survival rates of 89% and 45% (p less than 0.001) and 2-year survival rates of 64% and 15% (p less than 0.001), respectively. These rates remained significant when patients were stratified according to stage III or IV disease. Overall disease-free survival was also significantly prolonged in the GM-CSF group (p=0.03), although there was no difference between groups when stratified by stage of disease. Adverse events included transient myalgias, weakness, mild fatigue, rash, and mild erythema at injection siteSupport for using Leukine to treat pulmonary alveolar proteinosis can be found in a prospective, open-label study by Venkateshiah et al. Leukine therapy demonstrated good activity for the treatment of PAP. Patients (N=25; median age, 45 years; range, 21 to 57 years) with moderate disease were eligible for enrollment. Patients with a history of 2 or more lavages in the previous 4 months could also participate in the study at 3 months following their last whole-lung lavage (WLL) for a severe PAP exacerbation (n=21). Treatment consisted of Leukine 250 mcg/day subQ for the first month, 5 mcg/kg/day for the second month, and 9 mcg/kg/day for the third month. The Leukine dose could be increased to 12 mcg/kg/day at month 3, 15 mcg/kg/day at month 4, and 18 mcg/kg/day at month 5 if the patient was tolerating therapy but the response was suboptimal. When an adequate response was achieved, therapy could be continued for 3 to 12 months. At a mean follow-up of 39 +/- 17.3 months, 12 patients (48%) had an improvement in oxygenation with a 10 or greater mmHg decrease in the room air alveolar-arterial oxygen gradient (P(A-a)O2) (primary endpoint), with 8 patients not requiring WLL or home oxygen. Responders had significantly higher changes of PaO2, P(A-a)O2, diffusing capacity, total lung capacity, and 6-minute walk distance compared to patients who

did not respond to Leukine therapy. At 6 months, the responders also had significantly improved quality of life scores (assessed by the Short Form-36 questionnaire) from baseline compared to non-responders for all measures except bodily pain. Common adverse effects with Leukine therapy included injection-site reactions (redness (n=18), itching (n=11), swelling (n=12)), shortness of breath (n=10), and fatigue (n=7).

Support for using Leukine to treat rhinocerebral mucormycosis in a case series by Garcia-Diaz, Palau and Pankey. Three patients with non-neutropenic rhinocerebral zygomycosis were successfully treated with the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to traditional surgical and medical treatment. A 51-year-old woman with diabetes and bronchial asthma requiring steroid therapy developed sinusitis with left- sided face pain, periorbital swelling, erythema, and blurred vision; her left pupil was dilated and unresponsive to light, and she had a black nasal discharge. She received amphotericin B and an intranasal ethmoidectomy and medial maxillectomy; cultures showed Rhizopus species. The disease worsened with extensive bony sequestrum of the left maxilla and palate which was treated surgically. GM-CSF was added (total 4500 mcg), and the patient recovered with no recurrence in 4 years of follow-up. A 65-year-old man with diabetes and asthmatic bronchitis requiring steroid therapy developed right-sided maxillary pain and was found to have osteomyelitis. Histopathology of the maxillary bone was compatible with zygomycosis. He received amphotericin B but the disease progressed requiring debridement and right medial maxillectomy. His creatinine level increased; he received amphotericin B lipid complex (ABLC) and GM-CSF (425 mcg/day SC) and recovered with no recurrence with 3 years of follow-up. A 52-year-old woman with diabetes in ketoacidosis developed right eye pain and was found to have pansinusitis. She underwent right ethmoidectomy and removal of mucous membranes from right ethmoid and maxillary sinuses. Histology was consistent with zygomycosis. She received ABLC and GM-CSF 250 mcg/day SC but developed osteomyelitis of the right orbit requiring inferior orbitotomy. Histology was again consistent with zygomycosis. Treatment with ABLC and GM-CSF (total 45,000 micrograms) was discontinued approximately 5 months later as the patient was asymptomatic and biopsy showed no fungal elements; there was no recurrence in 2 years of follow-up.

Support for using Leukine for response enhancement following hepatitis B vaccination can be found in a study by Anandh, Bastani and Ballal. In chronic hemodialysis patients, granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjuvant therapy resulted in enhanced seroconversion after hepatitis B vaccinations. In a randomized study (n=28), patients who received GM-CSF 4-5 micrograms per kilogram (mcg/kg) 24 hours before the first dose of their initial series of 3 hepatitis B vaccinations (40 mcg each) had significantly higher antibody titers, and the seroconversion rate (5 of 6 patients) was higher than those randomized to receive vaccine alone (2 of 6). Another group of patients who had failed to seroconvert after their primary series were randomized to receive or not receive GM-CSF 24 hours before a booster dose of 40 mcg of vaccine. Significantly (p less than 0.02) more patients seroconverted after receiving GM-CSF before their booster (7 of 8) than those receiving booster alone (2 of 8) and antibody titers were significantly higher (p less than 0.05) in those who received GM-CSF. Side effects were few and minor. The GM-CSF product used in this study was not mentioned.

Support for using Leukine to treat metastatic renal cell carcinoma can be found in a study by Hotton et al. Treatment with a combination of interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) did not produce total tumor burden shrinkage of 50% or greater, or pulmonary metastases reduction of 50% or greater, in any of the 14 evaluable patients with renal cell carcinoma and pulmonary metastases in a phase Ib/II trial. Median survival had not been reached at time of publication; 6 of 16 patients died during approximately 14 months of follow-up. Six patients with prior nephrectomy and 10 patients without prior nephrectomy were enrolled. The study was discontinued when a 60-year-old woman with a history of polycythemia vera developed a grade 4 thrombocytopenia and multiple cerebral hemorrhages and died. Postmortem examination revealed acute multifocal cerebral venous thrombosis, hemorrhagic venous infarcts, subdural and subarachnoid hemorrhage, and thrombosis of the superior vena cava and renal veins. Other toxicities included transient lymphopenia, eosinophilia, and elevated prothrombin times in 2 patients

on warfarin therapy. Interleukin-2 was administered as a 96-hour continuous intravenous infusion on Days 1 through 4, days 8 through 11, and days 15 through 18 at a dose of 4.5 X 10(6) International Units/m(2) per day (27 of 31 total courses). GM-CSF was administered subcutaneously on days 8 through 19 at a dose of 1.25 mg/kg/day (12 of 31 courses) and 2.5 mg/kg/day (18 of 31 courses). There was a 14- to 19-day rest period between courses. The authors advise extreme caution with particular attention to early evidence of neurotoxicity in any further trials combining IL-2 and GM-CSF.

References

1. Leukine [package insert]. Lexington, MA: Partner Therapeutics, Inc.; August 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed June 5, 2024.
3. IBM Micromedex® DRUGDEX ® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com. (Accessed: June 6, 2024).
4. Lexicomp Online, AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; Accessed June 6, 2024.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf Accessed June 6, 2024.
6. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28):3199-3212.
7. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-3205.
8. Danyelza [package insert]. New York, NY: Y-mAbs Therapeutics, Inc.; March 2024.
9. Steward WP, von Pawel J, Gatzemeier U, et al: Effects of granulocyte-macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small-cell lung cancer: a prospective randomized study of 300 patients. J Clin Oncol 1998; 16(2):642-650.
10. Rospond RM, Glowacki RC, Mailliard JA. Sargramostim for sulfasalazine-induced agranulocytosis. Clin Pharm. 1993; 12:179.
11. Bjorkhom M, Pisa P, Arver S et al. Haematologic effects of granuloctye-macrophage colony stimulating factor in a patient with thiamazole-induced agranulocytosis. J Intern Med. 1992; 232:443-5.
12. Korzenik JR, Dieckgraefe BK, Valentine JF, et al: Sargramostim for active Crohn's disease. N Engl J Med 2005; 352(21):2193-2201.
13. Spitler LE, Grossbard ML, Ernstoff MS, et al: Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. J Clin Oncol 2000; 18(8):1614-1621.
14. Venkateshiah SB, Yan TD, Bonfield TL, et al: An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest 2006; 130(1):227-237.
15. Garcia-Diaz JB, Palau L, & Pankey GA: Resolution of rhinocerebral zygomycosis associated with adjuvant administration of granulocyte-macrophage colony-stimulating factor. Clin Infect Dis 2001; 32:e166-170.
16. Hotton KM, Khorsand M, Hank JA, et al: A phase Ib/II trial of granulocyte-macrophage--colony stimulating factor and interleukin-2 for renal cell carcinoma patients with pulmonary metastases: a case of fatal central nervous system thrombosis. Cancer 2000; 88(8):1892-1901.
17. Anandh U, Bastani B, & Ballal S: Granulocyte-macrophage colony-stimulating factor as an adjuvant to hepatitis B vaccination in maintenance hemodialysis patients. Am J Nephrol 2000; 20(1):53-56.

