Chemotherapy Observation or Inpatient Hospitalization (for Nebraska Only)

Policy Number: CS198NE.J
Effective Date: June 1, 2026

Instructions for Use

Table of Contents **Page**

Related Policies

- Elective Inpatient Services (for Nebraska Only)
- Hospital Services: Observation and Inpatient (for Nebraska Only)
- Mandatory Medicaid Coverage of Routine Patient Costs in Qualifying Clinical Trials (for Nebraska Only)

Application

This Medical Policy only applies to the State of Nebraska.

Coverage Rationale

Note: This policy does not apply to individuals under 18 years of age.

Most cancer chemotherapies can be administered safely and effectively in a physician's office or through home health care services. However, because of the risk of certain toxicities or individual comorbidities, some cancer chemotherapy may be administered either in a facility observation or inpatient unit.

An inpatient stay is medically necessary for drug regimens that require inpatient monitoring or complex administration over multiple days:

Regimen	Drugs	Factors contributing to the need for inpatient stay
EPOCH, DA-EPOCH, or R-EPOCH	• Etoposide 50 mg/m^2/day continuous infusion on days 1 to 4 • Prednisone • Vincristine (oncovin) IV days 1 to 4 • Cyclophosphamide 750 mg/m^2 IV on day 5 • Doxorubicin (hydroxydaunorubicin) 10 mg/m^2/day continuous infusion on days 1 to 4 • With or without rituximab	• Coordination of multiple infusions or multiple drugs over 96 hours
ESHAP or R-ESHAP	• Etoposide 40 mg/m^2/day continuous infusion on days 1 to 4 • Methylprednisolone (Solu-Medrol) • Cytarabine ("high-dose Ara-c") 2 g/m^2 • Cisplatin (Platinol) 25 mg/m^2 continuous infusion days 1 to 4 • With or without rituximab	• Coordination of multiple infusions or multiple drugs over 96 hours • Monitor for CNS toxicity with cytarabine

Regimen	Drugs	Factors contributing to the need for inpatient stay
Interleukin-2 infusion	• Interleukin-2 600,000 IU/kg IV every 8 hours for up to 14 consecutive doses over 5 days	• Continuous cardiac monitoring • Close monitoring of serum electrolytes, creatinine, bilirubin, and urine output • Vasopressor support with dopamine • Proximity to intensive care unit
High-dose ifosfamide	• Ifosfamide infusion > 1 g/m^2/day	• Close monitoring of serum electrolytes and urine pH • Replacement of electrolytes • Alkalinization of urine
High-dose methotrexate with leucovorin rescue	• Methotrexate dose at > 500 mg/m^2 • Leucovorin 15 mg every 6 hours for eight doses beginning 12 hours after the completion of methotrexate infusion and increased to 50 mg IV every 6 hours if methotrexate levels are > 20 µmol/L at 0 hour, are > 1.0 µmol/L at 24 hours, or are > 0.1 µmol/L at 48 hours after the end of methotrexate infusion, until levels are < 0.1 µmol/L plus	• Close monitoring of serum methotrexate levels
Hyper-CVAD	Cycles 1, 3, 5, and 7 (3-4 weeks between cycles): • Cyclophosphamide 300 mg/m^2 IV over 2 hours every 12 hours for six doses • Mesna 600 mg/m^2/day continuous infusion on days 1 to 3, starting 1 hour before cyclophosphamide • Vincristine • Doxorubicin 50 mg/m^2 IV on day 4 • Dexamethasone Cycles 2, 4, 6, and 8 (3-4 weeks between cycles): • Methotrexate 200 mg/m^2 IV over 2 hours followed by 800 mg/m^2 IV over 22 hours on day 1 plus • Cytarabine 3 g/m^2 (1 g/m^2 for individuals older than 60 years) IV over 2 hours every 12 hours for four doses starting on day 2 • Leucovorin 15 mg every 6 hours for eight doses beginning 12 hours after the completion of methotrexate infusion and increased to 50 mg IV every 6 hours if methotrexate levels are > 20 µmol/L at 0 hour, are > 1.0 µmol/L at 24 hours, or are > 0.1 µmol/L at 48 hours after the end of methotrexate infusion, until levels are < 0.1 µmol/L plus • Methylprednisolone 50 mg	• Coordination of multiple infusions or multiple drugs over 96 hours • Bladder irrigation with cyclophosphamide • Close monitoring of serum methotrexate levels

The following are clinical conditions or complications of cancer chemotherapy that may require an observation stay:

- Congestive heart failure or chronic renal failure requiring high-volume fluid infusions
- Known hypersensitivity reactions from previous infusion
- TACE (Transcatheter Arterial Chemoembolization) or intra-arterial chemotherapy infusion

The following are clinical conditions that require an inpatient hospital stay:

- Acute leukemia
- Intra-arterial infusion of chemotherapy
- Prophylaxis of tumor lysis syndrome in cases of high-grade lymphoma with large masses

Conditions requiring observation or inpatient hospital treatment other than those noted above will be reviewed on a case-by-case basis. For medical necessity clinical coverage criteria in these instances, refer to the InterQual® LOC: Acute

Adult, Hematology/Oncology: Complications or Disease Progression and/or InterQual® LOC: Acute Adult Hematology/Oncology: Treatments.

Click here to view the InterQual® criteria.

Notes:
- A written protocol will be expected to be followed by the provider administering the chemotherapy drug.
- Any requests for an extension of the inpatient stay beyond the recommended day(s) must be clinically reviewed.

Definitions

TACE (Transcatheter Arterial Chemoembolization): A procedure in which the blood supply to a tumor is blocked after anticancer drugs are given in blood vessels near the tumor (National Cancer Institute, 2022).

Description of Services

Chemotherapy uses drugs to treat cancer curatively or before (neoadjuvant) or after (adjuvant) other treatments such as surgery or radiation. It can also be used to slow cancer growth and relieve symptoms. Depending on a number of factors, including but not limited to the drugs being given, the route of administration, and a person's condition, chemotherapy can be administered at home, in a provider's office, in an outpatient clinic, or in the hospital (American Society of Clinical Oncology, 2022).

Clinical Evidence

Chellal et al. (2025) conducted a systematic review to highlight the critical role of therapeutic drug monitoring in managing high-dose methotrexate (HDMTX) therapy. The review encompassed thirty studies, with the majority focusing on quantifying methotrexate serum concentrations. The authors emphasized that monitoring methotrexate (MTX) levels is essential for reducing toxicity such as gastrointestinal, pulmonary, hepatic, and neurological side effects and for enhancing treatment efficacy, particularly in high-dose protocols. They report their findings underscore the need for vigilant surveillance to ensure patient safety and optimize clinical outcomes. The authors point out this study was limited by language restrictions, as it only included articles in English and French. Additionally, access to certain publications was not possible despite outreach efforts to the authors.

In a retrospective multicenter cohort study, Tirtei et al. (2024) assessed the efficacy and toxicity of high-dose 14-day ifosfamide (14-IFO) in patients with recurrent/refractory osteosarcoma (OS) treated in an outpatient (OP) setting. The primary end point was progression-free survival, while the secondary end points included disease control rate and the toxicity profile of 14-IFO. An additional exploratory end point was the estimation of the Growth Modulation Index. From January 2012 to December 2021, 26 patients with recurrent/refractory OS received at least one complete cycle of 14-IFO. Sixteen patients (61%) underwent at least four cycles. A total of 101 cycles were administered, all of which were evaluable for toxicity. No patient permanently discontinued treatment due to adverse events, although treatment delays occurred in seven patients (27%). Dose reductions were necessary for five patients (19%), primarily due to hematologic toxicities. The authors found that patients with relapsed OS exhibited a higher overall response rate of 45% and disease control rate of 82% compared with those with refractory OS, regardless of the number of previous treatment lines. Achieving disease control with 14-IFO allowed 27% of patients to receive new local treatments. The 4-month progression-free survival was 54% in all patients and 82% in the relapsed OS subgroup. Additionally, the authors reported that the results highlighted the manageable toxicity profile of the 14-IFO regimen, which allowed patients to receive chemotherapy at home, with scheduled clinical visits (every 3 or 7 days, depending on local practice), using an external elastomer pump for ifosfamide and mesna administration. The authors acknowledged that the Growth Modulation Index evaluation remains exploratory and that this study is limited by the small number of patients included in the analysis.

Nelles et al. (2023) evaluated the outcomes of treatment of double-hit lymphoma (DHL) with DA-EPOCH-R (dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in a retrospective cohort study. The authors conducted a retrospective study in 13 consecutive patients with DHL treated with DA-EPOCH-R in an OP tertiary center. The primary end points included complete response, event-free survival, and overall survival. Treatment was given in the OP setting where feasible, with admission to the inpatient (IP) unit as required for complications such as febrile neutropenia. The complete response rate with DA-EPOCH-R in DHL was 69% in the cohort. The median event-free survival and overall survival duration was 61 months (95% CI, 41-86 months) and 64 months (95% CI, 42-86 months), respectively. One patient discontinued DA-EPOCH-R due to recurrent febrile neutropenia, and there were no treatment- or infection-related deaths during the study. The authors concluded that DA-EPOCH-R is a well-

tolerated regimen for DHL that can be delivered primarily in an OP setting. They also noted that patient selection may be required to identify the cohort that is likely to tolerate dose escalation to derive full benefit from the protocol. The authors stated that further prospective studies are warranted to confirm these findings. The study is limited by a small number of patients and variations in adjunctive treatment.

In a retrospective cohort study, Banh et al. (2021) sought to characterize and compare both the outcome and cost of treatment of OP and IP ifosfamide therapy. The authors performed a single-center retrospective chart review of patients 18 years and older receiving ifosfamide therapy. The primary end point compared and evaluated the side effect profiles of ifosfamide-treated patients in the OP/IP settings. The adverse event grading system was characterized using the Common Terminology Criteria for Adverse Events version 5.0. The highest grade was documented per cycle. The secondary end point of this study compared the costs of OP/IP therapy. Ifosfamide therapy in 86 patients (57 OP; 29 IP) was reviewed. The predominant OP regimens were doxorubicin-ifosfamide-mesna with 43.9% and ifosfamide-etoposide with 29.8%. Grade 4 anemia, thrombocytopenia, and neutropenia were most frequent with IP vs. OP therapies (22.9% IP vs. 4.3% OP, 21.6% IP vs. 9.2% OP, and 22.8% IP vs. 19.6% OP, respectively). Neutropenic fever occurred in 20 OP patients, which was predominantly treated with doxorubicin-ifosfamide-mesna or ifosfamide-etoposide and led to an average hospital stay of 6 days. Neurotoxicity, treated with methylene blue, occurred in four OP patients. OP therapy saved a total of 783 hospital days. The authors concluded that transitioning ifosfamide to the OP setting is feasible for academic and community infusion centers, with the OP administration being safe, well tolerated, and associated with decreased total cost of care. This study was limited by a small sample size at a single institution and changes in the electronic medical record during the time period of the study. The authors also noted that it is possible that the patients who received therapy as an inpatient required closer monitoring, increasing the number of adverse drug events reported.

In a retrospective cohort study, Li et al. (2020) compared IP and OP administration of DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) in a single-center review. The study included patients with B-cell lymphoma who were 18 years or older and had received DA-EPOCH at Moffitt Cancer Center from April 26, 2017, through August 10, 2019. The primary end point was hospital admissions during OP chemotherapy (OPCT) administration. Additional safety end points included hospitalizations between cycles, infectious complications, extravasations, drug spills, pump malfunctions, and drug-related adverse events. Overall, 56 patients received 219 cycles of DA-EPOCH, with 193 cycles administered OP. Zero patients required hospitalization during OP administration of DA-EPOCH, resulting in 965 saved hospital days. In total, 23 patients (41%) were hospitalized between cycles, most commonly due to neutropenic fever (52%). No extravasations were documented throughout the study period. There were few incidences of drug spills or pump malfunctions. The authors concluded that routine OP administration of DA-EPOCH is both safe and feasible. The study is limited by the lack of a concurrent comparison group.

Chen et al. (2020) investigated differences in quality of life (QOL) in participants with esophageal squamous cell carcinoma (ESCC) who underwent IP chemotherapy (IPCT) or OPCT in a prospective cohort study. A total of 107 participants with ESCC were enrolled, including 53 participants in the IPCT group and 54 participants in the OPCT group. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items (QLQ-C30) and Oesophageal Cancer Module (QLQ-OES18) were used to examine the QOL in the two groups. In addition, the differences in adverse events were evaluated. The results of the QLQ-C30 analysis showed that mean global QOL scores were similar between the IPCT and OPCT groups, as were functional and symptom scales. There were no significant differences in the functional and symptom scales in the analysis of the QLQ-OES18 either. Most adverse events of chemotherapy were grades 1 to 2, and the majority of participants tolerated the side effects; no statistically significant difference in adverse events between these two groups was noted. The authors concluded that the health-related QOL and adverse events in participants with ESCC who received IPCT or OPCT were similar and that OPCT is reasonable and safe in clinical practice. This study is limited by a small sample size, which may have not allowed the detection of clinically significant differences, at a single institution with various chemotherapy interventions.

In a retrospective cohort study, Rodrigues et al. (2020) assessed the safety of consolidation with high-dose cytarabine in the OP setting. The authors retrospectively analyzed 39 patients who underwent consolidation with high-dose cytarabine between 2009 and 2018 at Ophir Loyola Hospital in Belém, Brazil. Patients treated after 2015 were given high-dose cytarabine as outpatients due to the decision by medical staff. Overall, 27 patients received 76 cycles of cytarabine as outpatients; male patients were 48.14% of the total population, with a median age of approximately 45 years. The occurrence of delay between cycles was significantly lower among outpatients (48.14% vs. 83.33%; $p = 0.04$). There was no difference in relapse rates, transfusion requirements, and nonrelapse mortality between both groups. Hospitalization was required in 40.74% of patients during OP cycles, and 18.51% of blood cultures were positive for pathogens. Nonrelapse mortality was significantly higher among patients above 50 years old and who were treated on an OP basis (44.4% vs. 5.60%; $p = 0.03$). The authors concluded that high-dose cytarabine administration on an OP basis appeared to be safe and effective in a low-income population in the Brazilian Amazon region, but toxicity seemed to be increased in patients older than 50 years. This study is limited by a small sample size in a single tertiary hospital.

In a case series, Keshvani et al. (2019) explored the economic and psychological impacts of transitioning EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)-based chemotherapy to an ambulatory infusion model. After receiving an initial cycle of chemotherapy in the hospital, study individuals received a rituximab infusion at the OP infusion center on day 1, followed by a combination solution of etoposide, vincristine, and doxorubicin that was replaced every 24 hours on days 2 to 4. After 96 hours of continuous infusion, individuals received a cyclophosphamide infusion at the clinic and received follow-up blood tests twice per week. From January 30, 2017, to January 30, 2018, 18 individuals received 61 cycles of EPOCH. The individuals reported improved QOL and a preference for home chemotherapy. They noted no chemotherapy vesicant extravasations and no unexpected adverse safety effects with OPCT infusion. The authors noted that the study is limited by a 50% response rate on the individuals' surveys and small sample size in a single-center study.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

ASCO and the Oncology Nursing Society assembled a multidisciplinary panel, including representatives from various organizations, to enhance the safety standards for chemotherapy administration. These guidelines, initially published in 2009 and updated in 2024, aim to provide a framework for best practices, minimize errors, and enhance efficiency. The 2024 updates include a shift in terminology from chemotherapy to antineoplastic therapy. Since the last major update in 2016, there has been a surge in new drugs and cancer treatment approaches, such as targeted therapies (mainly oral), immunomodulatory agents, bispecific T-cell engagers, and chimeric antigen receptor T-cell therapy, all of which are now included in the standards. Additionally, while antineoplastic therapy was traditionally administered in hospitals, physician's offices, or clinics, it is now increasingly common for treatments to be given at home or in independent centers with no direct affiliation to the prescribing physician. These updated standards emphasize the respective responsibilities of all parties involved. The 2024 guidelines are divided into the following sections: creating a safe environment; patient consent and education; ordering, preparing, dispensing, and administering oral and parenteral antineoplastic therapies in a health care facility, organization, or home; and lastly, monitoring during and after antineoplastic therapy is administered, including adherence, toxicity, and complications (Siegel et al., 2024).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA reviews data on a drug's safety and efficacy. FDA approval occurs once the data have been reviewed by the Center for Drug Evaluation and Research and it is determined that the benefit of the drug outweighs the potential risks in the intended population. Refer to the following website for information on FDA-approved drugs: http://www.accessdata.fda.gov/scripts/cder/daf/. (Accessed December 8, 2025)

References

American Society of Clinical Oncology (ASCO). Cancer.net. What is Chemotherapy? Available at: https://www.cancer.net/navigating-cancer-care/how-cancer-treated/chemotherapy/what-chemotherapy. Accessed December 8, 2025.

Banh C, Valsvik K, Arredondo A, et al. Transitioning ifosfamide chemotherapy regimens to the ambulatory setting: reviewing cost savings and safety profile. Support Care Cancer. 2022 Mar;30(3):2755-2766.

Chellal W, Metarfi Y, Ben Khadda et al. The interest of therapeutic and pharmacological drug monitoring of methotrexate: A systematic review. Semin Oncol. 2025 Apr;52(2):152342. Epub 2025 Apr 16.

Chen YH, Chen SW, Lu HI, et al. Similar quality of life and safety in patients receiving inpatient or outpatient chemotherapy: a focus on esophageal squamous cell carcinoma. Healthcare. 2020 Nov 1;8(4):447.

Keshvani N, Hon M, Gupta A, et al. Reducing hospitalizations: institution of outpatient infusional EPOCH-based chemotherapy at a safety net hospital. J Oncol Pract. 2019 Aug;15(8):e644-e651.

Li W, Richter KA, Tobon KA, et al. Safety and financial analysis of outpatient dose-adjusted EPOCH for B-cell lymphoma at a tertiary comprehensive cancer center. J Oncol Pharm Pract. 2021 Oct;27(7):1684-1690.

National Cancer Institute (NCI). TACE; 2022. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tace. Accessed December 8, 2025.

Nelles R, Morris K, Scott A, et al. Dose-adjusted-EPOCH-R is a safe and well tolerated outpatient treatment regimen in double-hit lymphoma. Intern Med J. 2023 May;53(5):773-778.

Rodrigues ALM, do Nascimento DM, de Lima JM, et al. Safety and feasibility of outpatient high dose cytarabine for acute myeloid leukemia in the Brazilian Amazon. Int J Hematol Oncol Stem Cell Res. 2020 Jul 1;14(3):151-156.

Siegel RD, LeFebvre KB, Temin S, et al. Antineoplastic therapy administration safety standards for adult and pediatric oncology: ASCO-ONS Standards. Oncol Nurs Forum. 2024 Jun 14;51(4):297-320.

Tirtei E, Campello A, Sciannameo V, et al. Prolonged 14-day continuous infusion of high-dose ifosfamide for patients with relapsed and refractory high-grade osteosarcoma: a retrospective multicentre cohort study. BMC Cancer. 2024 Jun 19;24(1):747.

Policy History/Revision Information

Date	Summary of Changes
06/01/2026	**Coverage Rationale** • Revised drug regimen requirements for an inpatient stay; removed list of applicable cancer type(s) for the listed regimens **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS198NE.I

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.