

Chemotherapy Observation or Inpatient Hospitalization

Guideline Number: MMG018.R

Effective Date: May 1, 2024

[Instructions for Use](#)

Table of Contents	Page
Coverage Rationale	1
Definitions	3
Description of Services	3
Clinical Evidence	3
U.S. Food and Drug Administration	5
References	5
Guideline History/Revision Information	6
Instructions for Use	6

Related Medical Management Guidelines
<ul style="list-style-type: none"> Clinical Trials Elective Inpatient Services Hospital Services (Inpatient and Outpatient)

Coverage Rationale

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

Most cancer chemotherapies can be administered safely and effectively in a physician’s office or through home healthcare services. However, because of the risk of certain toxicities or member co-morbidities, 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	Cancer Type	Factors contributing to the need for inpatient stay
EPOCH, DA-EPOCH, or R-EPOCH	<ul style="list-style-type: none"> Etoposide 50 mg/m²/day continuous infusion on days 1 to 4 Prednisone Vincristine (oncovine) IV days 1-4 Cyclophosphamide 750 mg/m² IV on day 5 Doxorubicin (hydroxydaunorubicin) 10 mg/m²/day continuous infusion on days 1-4 With or without Rituximab 	Lymphoma	<ul style="list-style-type: none"> Coordination of multiple infusions or multiple drugs over 96 hours
ESHAP or R-ESHAP	<ul style="list-style-type: none"> Etoposide 40 mg/m²/day continuous infusion on days 1 to 4 Methylprednisolone (solumedrol) Cytarabine (“high-dose Ara-c”) 2g/m² Cisplatin (platinol) 25mg/m² continuous infusion days 1-4 With or without Rituximab 	Lymphoma	<ul style="list-style-type: none"> Coordination of multiple infusions or multiple drugs over 96 hours Monitor for CNS toxicity with cytarabine

Regimen	Drugs	Cancer Type	Factors contributing to the need for inpatient stay
Interleukin 2 infusion	<ul style="list-style-type: none"> Interleukin 2 600,000 IU/kg IV every 8 hours for up to 14 consecutive doses over 5 days 	Melanoma, Renal Cell Cancer	<ul style="list-style-type: none"> Continuous cardiac monitoring Close monitoring of serum electrolytes, creatinine, bilirubin, urine output Vasopressor support with dopamine Proximity to intensive care unit
High dose Ifosphamide	<ul style="list-style-type: none"> Ifosphamide infusion > 1g/m²/day 	Sarcoma	<ul style="list-style-type: none"> Close monitoring of serum electrolytes and urine pH Replacement of electrolytes Alkalinization of urine
High dose methotrexate with leucovorin rescue	<ul style="list-style-type: none"> Methotrexate dose at > 500 mg/m² 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 	Lymphoma, Sarcoma	<ul style="list-style-type: none"> Close monitoring of serum methotrexate levels
Hyper-CVAD	<p>Cycles 1, 3, 5, and 7 (3-4 weeks between cycles):</p> <ul style="list-style-type: none"> Cyclophosphamide 300 mg/m² IV over 2 hours every 12 hours for 6 doses Mesna 600 mg/m²/day continuous infusion on days 1-3, starting 1 hour before cyclophosphamide Vincristine Doxorubicin 50 mg/m² IV on day 4 Dexamethasone <p>Cycles 2, 4, 6, and 8 (3-4 weeks between cycles):</p> <ul style="list-style-type: none"> Methotrexate 200 mg/m² IV over 2 hours followed by 800 mg/m² IV over 22 hours on day 1 plus Cytarabine 3 g/m² (1 g/m² for patients 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 	Lymphoma, Leukemia	<ul style="list-style-type: none"> 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 which may require an observation stay:

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

The following are clinical conditions which 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.

Note:

- 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. (NCI, 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, an outpatient clinic, or in the hospital. (ASCO, 2022)

Clinical Evidence

Nelles et al. (2023) evaluated outcomes of treatment of double-hit lymphoma (DHL) with dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) in a retrospective cohort study. The authors conducted a retrospective study of 13 consecutive patients with DHL treated with DA-EPOCH-R in an outpatient tertiary center. Primary endpoints included complete response (CR), event-free survival (EFS) and overall survival (OS). Treatment was given in the outpatient setting where feasible, with admission to the inpatient unit as required for complications such as febrile neutropenia. CR rate with DA-EPOCH-R in DHL was 69% in the cohort. Median EFS and OS 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 DA-EPOCH-R is a well-tolerated regimen for DHL that can be delivered primarily in an outpatient setting. They also noted that patient selection may be required to identify the cohort that are likely to tolerate dose escalation to derive full benefit from the protocol. The authors state that further prospective studies are warranted to confirm these findings. The study is limited by a small number of participants 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 outpatient (OP) and inpatient (IP) ifosfamide therapy. The authors performed a single-center retrospective chart review of patients 18 years and older receiving ifosfamide therapy. The primary endpoint 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 (CTCAE) Version 5.0. The highest grade was documented per cycle. The secondary endpoint of this study compares the costs of OP/IP therapy. Ifosfamide therapy of 86 patients (57 OP, 29 IP) was reviewed. The predominant OP regimens were doxorubicin-ifosfamide-mesna (AIM) with 43.9% and ifosfamide-etoposide (IE) with 29.8%. Grade 4 anemia, thrombocytopenia, and neutropenia were most frequent in 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 (NF) occurred in 20 OP patients which were

predominantly treated with AIM or IE and led to average hospital stay of 6 days. Neurotoxicity, treated with methylene blue occurred in 4 OP patients. OP therapy saved a total of 783 hospital days. The authors concluded 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 note that it is possible 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 dose-adjusted (DA-) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in a single center. The study included B-cell lymphoma patients who were 18 years or older and who had received DA-EPOCH at Moffitt Cancer Center from April 26, 2017 through August 10, 2019. The primary endpoint was hospital admissions during outpatient chemotherapy administration. Additional safety endpoints included hospitalizations between cycles, infectious complications, extravasations, drug spills, pump-malfunctions, and drug-related adverse events. Fifty-six patients received 219 cycles of DA-EPOCH with 193 cycles administered outpatient. Zero patients required hospitalization during outpatient administration of DA-EPOCH, resulting in 965 saved hospital days. Twenty-three 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 routine outpatient administration of DA-EPOCH is both safe and feasible. The study is limited by lack of concurrent comparison group.

Chen et al. (2020) investigated differences in quality of life (QoL) in esophageal squamous cell carcinoma (ESCC) patients who underwent inpatient chemotherapy (IPCT) or outpatient chemotherapy (OPCT) in a prospective cohort study. A total of 107 patients with ESCC were enrolled, including 53 patients in the IPCT group and 54 patients in the OPCT group. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items (EORTC QLQ-C30) and Oesophageal Cancer Module (EORTC QLQ-OES18) were used to examine the QoL of the two groups. In addition, the differences in adverse events (AEs) were evaluated. The results of QLQ C-30 analysis showed that mean global QoL scores were similar between 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 QLQ OES18 either. Most AEs of chemotherapy were grades 1-2, and the majority of patients tolerated the side effects; no statistically significant difference in AEs between these two groups was noted. The authors concluded that the health-related QoL and adverse events in ESCC patients who received IPCT or OPCT are similar and that OPCT is reasonable and safe in clinical practice. This study was limited by a small sample size, which may have not allowed to detect 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 outpatient 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 of medical staff. Twenty-seven patients received 76 cycles of cytarabine as outpatients; males 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 non-relapse mortality between both groups. Hospitalization was required in 40.74% of patients during outpatient cycles and 18.51% of blood cultures were positive for pathogens. Non-relapse mortality was significantly higher among patients above 50 years old and treated on an outpatient basis (44.4% vs. 5.60%, $P = 0.03$). The authors concluded high-dose cytarabine administration on an outpatient basis appeared to be safe and effective in a low-income population at the Brazilian Amazon region, but toxicity seems to be increased for patients older than 50 years. This study was 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 participants received a rituximab infusion at the outpatient infusion center on day one, followed by a combination solution of etoposide, vincristine, and doxorubicin that was replaced every 24 hours on days two to four. After 96 hours of continuous infusion, patients 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 patients received 61 cycles of EPOCH. The patients reported improved QoL and a preference for home chemotherapy. They noted no chemotherapy vesicant extravasations and no unexpected adverse safety effects with outpatient chemotherapy infusion. The authors noted the study was limited by a 50% response rate on the patient survey and small sample size in a single center study.

In a cross-over trial, Cox et al. (2011) compared patient preference for IP versus OP treatment with high-dose cisplatin (HDC). Secondary outcomes included aspects of health-related quality of life, adverse events (dose delays and reductions, elevated creatinine and unplanned readmissions) and resource use. Eligible patients were starting chemotherapy with ≥ 2 cycles of HDC (≥ 100 mg/dose) and were suitable for OP treatment. Exclusion criteria included previous treatment with cisplatin, a history of renal impairment or symptomatic heart failure, and pregnancy or lactation. All patients received an IP cycle and OP cycle: the order was randomly allocated. Pre-hydration, anti-emetics and chemotherapy were identical for IP and OP. Post-hydration varied by group (3 L normal saline (NS) for IP, 2 L NS for OP). Fifty-nine patients were randomized, 53 completed two cycles of HDC. Most patients preferred OP treatment (36 vs 13, $P = 0.002$). There were no significant differences in patients' ratings of nausea, vomiting, fatigue, anxiety, depression or overall quality of life. Adverse events were few and unrelated to IP versus OP treatment: There were nine unplanned hospital admissions after the 53 IP chemotherapy cycles and seven after the 53 OP cycles ($P = 0.428$). Nursing time was longer for IP than OP (163 vs 104 min, $P < 0.001$). The authors concluded most patient preferred OP treatment and OP treatment appeared safe and used less resources. This study is limited by the small sample size in a single center.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

The ASCO and the Oncology Nursing Society (ONS) worked together to create a set of chemotherapy administration safety standards. These guidelines were first published in 2009 and last updated in 2016 with the goal of providing a framework for best practice, reducing the risk of errors and increasing efficiency. The 2016 updated guidelines breaks the standards into four sections, creating a safe environment; treatment planning, patient consent, and education; ordering, preparing, dispensing, and administering chemotherapy; and lastly monitoring after administration of chemotherapy. These standards were intended to be used in a variety of settings and patient populations, but do not address specifically which setting is appropriate in different clinical situations. (Neuss et al., 2017)

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 drug's safety and efficacy. FDA approval occurs once the data has been reviewed by the Center for Drug Evaluation and Research (CDER) 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 November 30, 2023)

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 November 30, 2023.
- 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.
- 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.
- Cox KM, Goel S, O'Connell RL, et al. Randomized cross-over trial comparing inpatient and outpatient administration of high-dose cisplatin. *Intern Med J*. 2011 Feb;41(2):172-8.
- 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 12, 2023.

Nelles R, Morris K, Scott A, Kennedy G. 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.

Neuss MN, Gilmore TR, Belderson KM, et al. 2016 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards, including standards for pediatric oncology. *Oncol Nurs Forum.* 2017 Jan 6;44(1):31-43.

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.

Guideline History/Revision Information

Date	Summary of Changes
05/01/2024	<p>Related Policies</p> <ul style="list-style-type: none"> Added reference link to the Medical Management Guideline titled <i>Hospital Services (Inpatient and Outpatient)</i> <p>Coverage Rationale</p> <ul style="list-style-type: none"> Revised medical necessity clinical coverage criteria for conditions requiring observation or inpatient hospital treatment other than those noted [in the policy]: <ul style="list-style-type: none"> Added reference to the: <ul style="list-style-type: none"> InterQual® LOC: Acute Adult, Hematology/Oncology: Complications or Disease Progression InterQual® LOC: Acute Adult, Hematology/Oncology: Treatments Removed reference to the InterQual® LOC: Acute Adult, Hematology/Oncology: Chemotherapy <p>Supporting Information</p> <ul style="list-style-type: none"> Updated <i>References</i> section to reflect the most current information Archived previous policy version MMG018.Q

Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline 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. UnitedHealthcare West Medical Management Guidelines 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.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.