Transitioning Select Chemotherapeutics to the Outpatient Setting Improves Care and Reduces Costs

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As those of us in oncology have seen over the years, the cost of chemotherapy across the board continues to rise. In some cases, oncology drug prices increased at an exponential rate. Looking at anti-cancer drug costs at time of U.S. Food and Drug Administration approval from 2014 to 2019, these costs surpassed the $10,000 range and are close to a cost of $100,000 per one month of treatment.[1]

But anti-cancer medication prices are not the only healthcare-related costs. Some patients with cancer also incur costs related to inpatient bed stays for chemotherapy administration. In some cases, patients who are treated in the inpatient setting may be admitted to the hospital and must wait before treatment can start—adding to an already high bill. Due to scheduling mishaps or late arrivals, patients may also end up paying for extra days spent in the hospital for treatments that can be safely administered in the outpatient setting. Figure 1, page 58, shows the average costs of inpatient bed stays per day across the United States and within Arizona.[2] Since the cost of cancer care continues to rise and many patients now face financial toxicity, we, as members of the cancer care team, need to address costs across the care continuum to help patients achieve better outcomes and to decrease costs to patients and to cancer programs and practices. This includes addressing inpatient stays and transitioning administration of certain chemotherapeutic agents to the more cost-effective outpatient setting.

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Why the Move to the Outpatient Setting?

Moving chemotherapy administration from the inpatient to the outpatient setting has been a popular conversation in oncology for decades. Since 1996, various justifications were made to keep patients in the hospital when they receive chemotherapy treatment; for example, special procedure chemotherapy, high-dosage chemotherapy, and induction therapy.[3] We can see how oncology has changed in the past 25 years because many of these inpatient chemotherapy regimens can now be safely given in the outpatient setting. More so, appropriate chemotherapy administration in

Figure 1. Average Cost of Inpatient Bed Stay[2]

United States

- State/local government hospital: $1,878 in 2015 and $2,052 in 2020.
- Non-profit hospital: $2,289 in 2015 and $2,488 in 2020.
- For-profit hospital: $1,791 in 2015 and $1,889 in 2020.

Arizona

- State/local government hospital: $2,089 in 2015 and $2,034 in 2020.
- Non-profit hospital: $2,474 in 2015 and $2,675 in 2020.
- For-profit hospital: $1,035 in 2015 and $1,959 in 2020.

the outpatient setting has many benefits to patients and the cancer program, including:

- Reducing the cost of chemotherapy.
- Relieving inpatient bed crunch.
- Making patients eligible for patient assistance options (e.g., pharmaceutical patient assistance programs or co-pay assistance programs).
- Allowing cancer programs and practices to bill for waste.
- Improving overall patient satisfaction.

Outpatient chemotherapy administration also reduces costs to the cancer program or practice and our overall healthcare system. Patients no longer need to pay for unnecessary bed stays, and inpatient beds will be available in the hospital for those who truly need them. This benefit was especially true during the COVID-19 pandemic.[4] Oncology patients are often immune compromised and face the risk of infection, especially when admitted into the hospital. By keeping these patients in the outpatient setting, we reduce their risk of infection and remove costs associated with expensive inpatient stays.

In the outpatient setting, more patients are also eligible and qualify for patient assistance and co-pay programs offered by drug manufacturers or independent foundations. Therefore, with help from your financial navigation team, you can continue to reduce patients' cost of care.

Drug waste cannot be billed in the inpatient setting. Revenue is often lost from inpatient chemotherapy administration because payments are subject to diagnosis related groups (set rates established by Medicare for the operating costs of hospital inpatient stays under Medicare Part A),[5] and high-cost chemotherapies often are not adequately reimbursed. Because of the "buy-and-bill" philosophy that many inpatient settings follow, a cancer program or practice ends up eating the costs of drug waste because they are not reimbursable.

Chemotherapy administration in the outpatient setting has been shown to be safe and effective, and some providers find it to be a much easier setting in which to treat patients. The outpatient setting also respects patients' wishes to avoid hospitalization and provides patients immediate and direct control of their therapy administration. In addition, outpatient chemotherapy administration decreases the overall costs of inpatient chemotherapy, reduces overnight stays or avoids hospital admissions, and can lead to an improvement in long-acting nausea and vomiting control, infusion pump use, and supportive care medication administration to prevent overnight stays.

For certain patients, however, it is still best to administer chemotherapy in the inpatient setting, such as those with acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML), those who have been newly diagnosed, or those with urgent conditions for solid tumors or allogeneic transplant and some chimeric antigen receptor (CAR) T-cell therapies. This way patients receive around-the-clock acute care management in case of toxicity.

What Do Patients Want?

Providers and staff at the University of Arizona Cancer Center, along with published literature, report that patients want to receive their therapies in the outpatient setting when possible. Below are examples of patient feedback we received:

- "I get no sleep when I'm admitted, so I hate staying inpatient."
- "I waited eight hours for a bed to get admitted and start chemotherapy the next day."
- "I have kids, so I do not have time for an inpatient stay."
- "I have a line attached to my arm for three days for only two days of chemotherapy."

Patient feedback and the need to improve patient satisfaction were the main reasons why we began looking at chemotherapy regimens that could be safely administered in the outpatient setting. Based on these clinical and patient needs, our first task was to determine the right patients and the right chemotherapy regimens to administer in the outpatient setting.

Selecting the Outpatient Chemotherapy Regimens

When choosing which chemotherapies to transition to the outpatient setting, we first looked at rituximab and clofarabine.[6,7] In 2013, we were using a lot more clofarabine and, in these cases, patients did not have access to patient assistance programs, there was drug waste that we could not bill for, and patients often had to wait until the next day to start chemotherapy due to their arrival time. In some cases, there was need for 24-hour observation prior to starting treatment and we sometimes experienced a lack of signed chemotherapy orders on the day of treatment. Patients who did arrive on time would sometimes have to wait until the next day to be treated so a physician could evaluate them and sign the order.

High dose cytarabine (HiDAC) is a chemotherapy regimen used to treat patients with acute myeloid leukemia and can be

used in combination or as a monotherapy.[8] In the outpatient setting, we provide HiDAC under a general infusion schedule to patients who are deemed to be reliable, are compliant, and have suitable transportation. It is a multi-day regimen, so we usually begin treatment on a Monday morning to ensure treatment completion occurs during normal infusion center hours. Originally, transition of this chemotherapy regimen was done in phases (e.g., we started by providing the third or fourth cycle in the outpatient setting), but now we provide all four cycles of treatment in the outpatient setting (Table 1, below).

Looking at rituximab, we decided to adopt a hybrid inpatient-outpatient administration model, similar to our phased approach of administering HiDAC in the outpatient setting. A typical example of a rituximab chemotherapy is the rituximab, ifosfamide, carboplatin, and etoposide in combination (R-ICE) regimen (Table 2, page 60). We administer ifosfamide, carboplatin, and etoposide (ICE) in the inpatient setting and when patients are discharged, and then on day three or four patients come in to get their rituximab and pegfilgrastim or its biosimilar in the outpatient clinic. An example of an outpatient rituximab hybrid regimen with inpatient chemotherapy is listed in in Table 3, page 60.

Since 2015 when we transitioned certain rituximab administrations to the outpatient setting, we decreased our inpatient bed stays, reduced our inpatient chemotherapy costs, and increased the use of our own specialty pharmacy for patients receiving intravenous rituximab combination regimens, as well as an increased use of this model post-implementation for standard order sets. However, not every patient receiving rituximab can be treated in the outpatient setting. Accordingly, we have developed patient restrictions for rituximab in the outpatient setting, including:

- Immune thrombocytopenic purpura—dose-reduced rituximab, 100 mg[9].
- Cold agglutinin disease.
- Post-transplant lymphoproliferative disease.
- Autoimmune hemolytic anemia.
- Prolonged chemotherapy inpatient stays requiring continued treatment.
- Infusion reaction or need for rituximab desensitization.

A third example is the etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin in combination (EPOCH) chemotherapy regimen (Table 4, page 61). EPOCH is given for numerous indications, including diffuse large b-cell lymphoma. In transitioning this chemotherapy regimen to the outpatient setting, we developed a workflow utilizing our smart pump technology—a major change from what was previously done.

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Table 1. The University of Arizona Outpatient HiDAC Workflow

	Monday	Wednesday	Friday
Days of therapy	1	3	5
07:00	Neuro-check/antiemetics	Neuro-check/antiemetics	Neuro-check/antiemetics
07:30	HiDAC	HiDAC	HiDAC
Infusion	1 hour	1 hour	1 hour
Discharge	—	—	—
16:00	Neuro-check	Neuro-check	Neuro-check
16:30	HiDAC	HiDAC	HiDAC
Infusion	1 hour	1 hour	1 hour
Pegfilgrastim	—	—	+/- Pegfilgrastim or pegfilgrastim-cbqv
Premedications (30 minutes before infusion)	Ondansetron 8 mg (IV) Dexamethasone 10mg (PO)	Ondansetron 8 mg (IV) Dexamethasone 10mg (PO)	Ondansetron 8 mg (IV) Dexamethasone 10mg (PO)
At home medications	Acyclovir, promethazine, dexamethasone ophthalmic suspension		

Table 2. Transitioned Ifosfamide-Based Regimens[a]

Disease State	Chemotherapy Regimen
Sarcoma	AIM
	IE
	AEWS 1031/1221
Germ cell tumors	TIP
	VIP
	ACNS 1123
	TI
	VeIP
Lymphoma	IGEV
	ICE
	R-ICE
	IVAC
	VIPD
	SMILE
	GIFOX
Lung cancer	Ifosfamide (monotherapy)

Note: AIM = doxorubicin, ifosfamide, mesna; IE = ifosfamide, etoposide; TIP = paclitaxel, ifosfamide, cisplatin; VIP = etoposide, ifosfamide, cisplatin; IGEV = ifosfamide, gemcitabine, vinorelbine; ICE = ifosfamide, carboplatin, etoposide; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; IVAC = ifosfamide, etoposide, cytarabine; SMILE = dexamethasone, methotrexate, leucovorine, asparapinase, etoposide; AEWS1031/1221 = vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide; ACNS1123 = carboplatin, etoposide, ifosfamide; TI = paclitaxel, ifosfamide.

[a]Some patients had alternating ifosfamide-containing regimens.

Table 3. Hybrid-Based Regimens with Rituximab[a]

Disease State	Chemotherapy Regimen
Lymphoma	CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)
	Mini-CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)
	COEP-R (cyclophosphamide, vincristine, etoposide, prednisone, rituximab)
	CHOEP-R (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, rituximab)
	CVP-R (cyclophosphamide, vincristine, prednisone, rituximab)
	ICE-R (ifosfamide, carboplatin, etoposide)
	ESHAP-R (etoposide, methylprednisolone, cytarabine, cisplatin, rituximab)
	DHAP-R (dexamethasone, cytarabine, cisplatin, rituximab)
	CVAD-R (cyclophosphamide, vincristine, doxorubicin, dexamethasone, rituximab)
	EPOCH-R (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone, rituximab)
	CODOX-M-R (cyclophosphamide, vincristine, doxorubicin, cytarabine, high-dose methotrexate, rituximab)
	MPV-R (high-dose methotrexate, procarbazine, vincristine, rituximab)
	BR (Bendamustine Rituximab)
	PBR (Bendamustine Polatuzumab Rituximab)
	MATRix regimen (methotrexate, cytarabine, thiotepa, rituximab)
Acute Lymphocytic Leukemia (ALL)	HCVAD-R (course A regimen: cyclophosphamide, vincistine, doxorubicin, dexamethasone, rituximab; course B regimen: high-dose methotrexate, cytarabine, rituximab)
	CD20+ ALL regimens

[a]Patients who required combination chemotherapy were administered the backbone chemotherapy regimen inpatient, and then administered rituximab outpatient the following day.

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Therefore, we needed to address monitoring parameters and eventually decided to do labs at the initiation of chemotherapy. (In the inpatient setting, patients get labs done every day, which increases their costs.) Our clinical ambulatory oncology pharmacists ensure that patients receive the correct take-home medications prior to treatment initiation. So, by administering the full EPOCH regimen in the outpatient setting, we are realizing cost savings for patients and the hospital.

Selecting the Patients to Treat in the Outpatient Setting

As mentioned with the rituximab regimens, not every patient should receive their chemotherapy treatment in the outpatient setting. When looking at our patients, we developed criteria that continue to be refined today to make sure we are treating the appropriate patients with outpatient chemotherapy (Table 5, page 62). For example, at the University of Arizona Cancer Center, we treat patients who travel across the state, so we did not want to move these patients to the outpatient setting if they have excessive travel time or unreliable transportation. We chose patients who have a good support system at home and who are often accompanied by their caregiver(s) during treatment. Finally, to provide the quality care that patients with cancer need, we set up after-hours care since patients would no longer receive the 24-hour care they had gotten in the inpatient setting. We used oncology fellows and nurses to address triage calls and the pharmacy clinical coordinator to address urgent chemotherapy issues.

We also introduced an on-call service for patients using infusion pumps. This was key to developing our outpatient chemotherapy orders because pumps are required for certain chemotherapy regimens such as EPOCH; vincristine, doxorubicin, and dexamethasone in combination (VAD); doxorubicin 24-hour infusions; cytarabine infusions; and ifosfamide orders. We evaluated our workflows to include the necessary steps for administering and checking infusion pumps, as well as using our rental pumps on-call service number. Pumps are often controlled by the state's board of pharmacy law, which required some research. For example, in Arizona, every time a pump leaves the clinic, we must complete a regulatory check. Therefore, we included this step in our outpatient workflows. We also did education with patients and caregivers on their infusion pumps and any issues that could arise, including information about the on-call service for needs that came up after hours. To this day, infusion pumps continue to pose challenges, so we set up a workflow for four oncology fellows to call a pharmacist on staff to address any issues that crop up after hours. Our outpatient treatment utilizes same-day pegfilgrastim or pegfilgrastim-cbqv for ease of use in our patients and previous studies in lymphoma showed similar efficacy without undue febrile neutropenia risk.[10,11] In our studies, we evaluated same-day versus next-day pegfilgrastim and found similar outcomes of febrile neutropenia incidence, regardless of the originator or reference product. Recent studies have yielded equivocal outcomes of febrile neutropenia incidence with same-day versus next-day administration.

Developing Our Practice Model

When looking at designing and implementing any new models of care, you first need to develop a practice model, which takes teamwork. In our case, we first evaluated our high-cost inpatient chemotherapy regimens (e.g., R-ICE, EPOCH) (Table 4, below). This was done via weekly and then monthly meetings with pharmacy leadership: the pharmacy manager and clinical pharmacy team. In these meetings, we evaluated inpatient and outpatient chemotherapy trends and identified in what settings certain chemotherapies were being administered. We came to realize that chemotherapy was often administered in the inpatient setting just because it could be—and that trend was consistent across the board. Finally, we reviewed our pharmacy budget every month, so we could calculate costs and the impact of transitioning certain

Table 4. Outpatient Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, and Rituximab (DA-EPOCH +/- ¬R) Regimena (Dosages Are Based on Dose Level One)

Drug	Dose and Route	Given on Day(s)
Rituximab	37 mg/m^2 IV	1
Etoposide	50 mg/m^2 per day IV	1-4 (96 hours)
Doxorubicin	50 mg/m^2 per day IV	
Vincristine	0.4 mg/m^2 per day IV (dose not capped)	
Cyclophosphamide	75 mg/m^2 IV	5
Pegfilgrastim or pegfilgrastim-cbqv	6 mg	5

Table 5. Criteria for Patient Selection for Outpatient Chemotherapy[a]

Criteria	Patient and Caregiver Evaluation
Patient	Able to understand chemotherapy and supportive care management
	Has a caregiver or caregiver support during chemotherapy infusion and support visits
Location	Patient must live within approximately 30 minutes of our infusion center sites
Transportation	Patient must have transportation to and from the infusion center for treatment
Clinical management in outpatient clinic	Patient must be able to be assessed by the physician or advanced practitioner at least once a week in the outpatient clinic
	Lab monitoring done twice a week or more frequently if needed
Supportive care medication	Patient must have treatment/supportive care medications prior to start of infusion and before therapy (HiDAC dexamethasone eye drops; EPOCH prednisone therapy)
After hours care	Patient or caregiver must be able to recognize toxicity profiles of chemotherapy (HiDAC neurotoxocity, clofarabine infusion reaction/cytokine release)
	Patient or caregiver must understand pump infusion and support services for home administration of infusion therapies

[a]Patients are evaluated for outpatient care based on several criteria to ensure adherence to therapies and maintain patient safety with chemotherapy issues that were set up prior to the transition for outpatient chemotherapy treatments.

chemotherapeutic administrations from the inpatient to outpatient setting.

In moving administration of select chemotherapy regimens to the outpatient setting, we wanted to improve patient care overall at our facility. This required buy-in from the multidisciplinary cancer care team—physicians, advance practitioners, fellows, nursing staff, pharmacy staff, and the financial team. We had to address these outpatient options early and educate staff on these treatments. Our nurse coordinators in the clinic needed to evaluate the treatments we wanted to move to the outpatient setting, which included addressing each anti-cancer drug, any supportive care needs, and any follow-up lab tests. Our financial team was one of the critical pieces in the early assessment discussions. They knew that they would have to address outpatient chemotherapy with payers and, in some cases, pharmacists and physicians would need to step in and educate payers about which treatments could be given safely in the outpatient setting. The finance team worked on denials and addressed them quickly. Our clinical pharmacists and staff pharmacists addressed patient eligibility for outpatient chemotherapy and supportive care services. These pharmacists review all medications, including any supportive care medicines, or any relevant lab tests.

Beginning in 2013, we began transitioning administration of select chemotherapy regimens to the outpatient setting. We first implemented this transition into our electronic health record (EHR), creating the necessary order sets for the selected chemotherapies and establishing these processes as a formal workflow using our EHR. Because we started this project in 2013, shortly after moving to a new EHR, we had to set up these processes—regardless of access to an EHR. These processes included the use of standardized antiemetics and appropriate tests.

As mentioned above, implementation of this model was a team effort. It included our medical director, physicians and providers, nurse coordinators, oncology ambulatory specialists, finance team, financial counselors, nurse navigators, infusion center management, staff pharmacists, information technology team, and risk management. Everyone was involved in the process and everyone had a part to play, which speaks to the diversity and strength of our healthcare team at the University of Arizona Cancer Center when addressing and implementing practice change.

Our medical director addressed any patient-related issues for those who needed inpatient chemotherapy, as well as any other resolutions needed for larger program-wide issues. Our physicians and nurses ensured there was housing available for patients who had to travel, working with our supportive staff to address housing and fuel assistance. One of the more amazing pieces of this project was seeing our infusion nurses drive home the need for this transition. Because many were former bone marrow transplant

nurses, they made the transition from inpatient to outpatient easily and were already aware of some of the chemotherapies they would be working with. The clinical ambulatory pharmacists also set up an education opportunity for our nurses to ensure they knew about treatment toxicities and side effects of the chemotherapies that would now be administered in the outpatient setting. Our nurse coordinators then addressed any issues related to outpatient chemotherapy timing and scheduling.

Other key members of the team included our clinical pharmacy staff. They addressed some of the educational pieces for other staff and patients, worked with supportive care, and led treatment adherence. Pharmacists also worked on some of the chemotherapy regimen builds within the EHR. Finally, our staff pharmacists addressed any billing issues, performed dose rounding, billed for waste, and helped with the overall transition from the inpatient to the outpatient setting. Additionally, the staff pharmacists established our outpatient care hours for early morning administration. Today, we open earlier than the hospital for our outpatient high-dose cytarabine-containing regimens. Since the transition of cytarabine to the outpatient setting, we have been able to move several other AML regimens to the outpatient setting (Table 6, right).

Figure 2, right, shows an example checklist for transitioning administration of selected chemotherapy to the outpatient setting. Following this checklist will ensure that you have financial approval, including:

- Coverage of infusion pumps.
- Infusion hours set up in case a schedule prohibits the administration of certain chemotherapy agents.
- Nursing staff to lead the education of any coordinators or infusion nurses.
- Pharmacy and specialty pharmacy to educate staff on regimens and supportive care treatments.

Measure, Measure, Measure

As you should for any new program, measuring outcomes and cost savings proves the impact that your innovation has on your patients and cancer program. As my former University of Arizona Cancer Center director Peter Drucker used to say, "If I can't measure it, I can't manage it." In developing this program, our team knew it needed to gather metrics and identified the following areas to measure:

- High-cost chemotherapy regimens administered in the inpatient setting.
- Chemotherapy administration transitioned from the inpatient to the outpatient setting.
- Inpatient days per admission.
- Medication assistance program dollar amounts.
- Patient outcomes.
- Miscellaneous data, such as emergency department (ED) visits, hours between inpatient admission and chemotherapy start, and length of time for each day of outpatient chemotherapy.

Table 6. Transitioned Outpatient Myeloid Regimens, Including Outpatient Acute Myeloid Leukemia and Acute Lymphocytic Leukemia

Disease State	Chemotherapy Regimen
AML	5+2
	ME/MEC
	FLA/FLAG
	CLA/CLAG
	HiDAC
	Clofarabine
	Clofarabine/HiDAC
ALL	Clofarabine

Figure 2. Example Outpatient Chemotherapy Transition Checklist

- **Selected chemotherapy available to be administered outpatient**
- **Financial approval**
  - **Infusion pumps covered**
- **Infusion center hours**
  - **Current schedules prohibit administration of certain chemotherapeutic agents**
- **Nursing staff**
  - **Education with nurse coordinators**
  - **Education with infusion nurses on administration and side effect monitoring**
- **Pharmacy/specialty pharmacy**
  - **Education on regimens and supportive care treatments**
  - **Large focus on anti-infective prophylaxis**

For rituximab, our original benchmark goal at implementation was 90 percent outpatient administration. Since then, we transitioned 137 of 173 (79 percent) patients receiving rituximab to the outpatient setting. Initial inpatient rituximab savings to our cancer program include drug cost savings between $400,000 and $450,000, and an average inpatient bed stay decrease of approximately nine hours. Therefore, our cancer program and hospital are saving about $950,000 annually for administering rituximab in the outpatient setting.

For patients who received an EPOCH-based chemotherapy regimen, out of 175 cycles, there were 18 cycles that were administered inpatient for a total cost of $89,857. With the transition of 67 cycles to a hybrid inpatient/outpatient setting, we realized a cost savings of $180,453 and saved 67 hospital bed days. Ninety cycles were transitioned fully to the outpatient setting with a cost savings of $1,454,398 and 540 hospital bed days. Overall, by transitioning to a hybrid inpatient/outpatient or outpatient setting, the updated total cost savings for hospital stay, drug cost and labs, under an alternative payment model, was $3,523,174 with 607 hospital bed days saved.

Looking Toward the Future

We continuously work to safely transition more chemotherapy regimens to the outpatient setting, especially as our hospital and patients have realized cost savings and improved satisfaction. Our next list of chemotherapies to consider for transition, includes:

- HyperCVAD, Part A.
- Dexamethasone, cyclophosphamide, etoposide, and cisplatin in combination (DCEP); and bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide in combination (VTD-PACE).
- Outpatient stem cell transplant conditioning regimens, including thiotepa/carmustine; melphalan; and carmustine, etoposide, cytarabine, and melphalan in combination (BEAM). OI

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