ASTCT 2022 National Fludarabine Shortage for HCT and CAR-T Cell Recipients: Frequently Asked Questions

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Introduction

Fludarabine is a common chemotherapy agent utilized in a multitude of conditioning regimens prior to hematopoietic cell transplant (HCT) and for lymphodepletion prior to chimeric antigen receptor (CAR) T-cell therapy. As of May 2022, fludarabine was reported to be in short supply in the United States. There are five companies that supply fludarabine, of which the reason for the shortage is unknown. One company has reported a shortage due to manufacturing delays while another due to increased demand. In August of 2020, Pfizer discontinued manufacturing fludarabine though their market share was less than 1%. As a result of the national shortage, many institutions find themselves with a difficult dilemma in how they continue to treat patients.[1] This FAQ will address various questions institutions may have as they work through difficult decisions and analyze the available literature with alternative conditioning and lymphodepleting regimens that do not contain fludarabine.

Helpful websites to stay up to date with the ongoing shortage:
American Society of Health-System Pharmacists (ASHP) Fludarabine Shortage
FDA Drug Shortage Database

Section A: Conservation Efforts of Fludarabine Supply

Implementation of various strategies to conserve supply is the usual initial step in management of drug shortages. The typical methods used include dose rounding, batching of doses, extending beyond use dating, and patient prioritization. A review of these methods is discussed below.

1) Dose Rounding
   Most intravenous cytotoxic chemotherapy agents are supplied in single-use vials, meaning the vial is meant to be used for a single patient or single case/procedure (CDC Injection Safety). Therefore, dose rounding to the nearest vial size is a widely accepted means to conserve drug supply and reduce waste by preventing the use of partial vials. Guidance from the Hematology Oncology Pharmacists

Association regarding cytotoxic agents allows for rounding to a standard vial size if within 10% of the calculated dose. In the case of fludarabine, all U.S. manufacturers supply the drug in a 50 mg vial. Therefore, using 10% as the maximum for rounding, patients requiring a calculated dose of >50 mg but <55 mg can be rounded down to a 50 mg to use only a single vial.

2) Dose Batching
When dose rounding is not possible, dose batching also helps reduce wasting of partial vials. This is done by preparing all doses for the institution at the same time to conserve vials. This can even be taken a step further where patients can be scheduled on certain days to further minimize waste, for example, scheduling 5 patients to receive fludarabine on the same day, instead of 2 on one day and 3 on another day, especially if their combined calculated doses can be made using multiple full vials with no partial vials needed. For larger health systems with multiple hospitals or satellite clinic locations, it may also be helpful to consider stocking and compounding fludarabine at one central location and distributing doses out to other hospitals and locations. This can further maximize dose batching efforts as well as facilitate more accurate tracking and use of supply throughout the entire health system.

3) Extended Beyond Use Dating
Another method that can be employed to conserve supply is to utilize extended beyond use dating for vials. Vials of fludarabine are typically recommended per the manufacturer package insert to be used within 8 hours of vial puncture. However, there are data supporting stability at a concentration of 1 mg/mL in normal saline for up to 16 days.[2] Therefore, compounding and storing the drug in this manner can also be used as a measure to save drug for future use if a full vial is not able to be used for a given patient or across multiple patients on the same day.

4) Prioritization (ethics)/Minimizing use in non-HCT/CAR-T use
In the event that the above conservation methods do not allow for all patients to be treated with fludarabine, consideration can be given to implementation of patient prioritization. Supply can then be reserved for regimens/patients where alternative options to fludarabine are unavailable or not otherwise suitable. For example, since there are limited data for alternative agents for CAR-T lymphodepletion[3-5], many centers are prioritizing use for these patients and using alternative regimens for other diagnoses where use of fludarabine may be less critical. It is highly recommended that if patient prioritization is being done that hospital legal and ethics personnel are involved. A committee can be formed that is comprised of pharmacy and physician leaders as well as legal and ethics to determine the most appropriate prioritization strategy and communicate it with both providers and patients.

5) Investigational Studies
Consideration must also be given for clinical trials that utilize fludarabine. There can be significant implications for usage based on whether the drug needs to come from hospital/commercial supply or whether it is supplied by the trial sponsor. If it is commercially supplied, this should be factored into any prioritization efforts the health system implements. If supply cannot be maintained, then

consideration for pausing trial enrollment should be made. Some centers have referred patients for treatment to other hospitals that are sites for the same clinical trial if they have adequate supply of fludarabine to accommodate additional patients.

Section B: Conditioning Regimens for HCT Recipients

Herein, we briefly describe the published literature for conditioning regimens in HCT and lymphodepletion in CAR-T. Please note, the highlighted trials are meant to be informative for institutes to allow patients/providers to make individualized treatment decisions based on the available evidence and be tailored for individual patients. We do not specifically recommend a specific regimen over another.

1) What myeloablative conditioning regimens are available for matched donor transplants (sibling or unrelated)?

Combination fludarabine and busulfan conditioning has become a widely adopted standard myeloablative regimen across institutions due to various studies demonstrating similar efficacy outcomes with less toxicity compared to other myeloablative regimens-namely busulfan/cyclophosphamide. Busulfan/cyclophosphamide could be a potential alternative to fludarabine/busulfan if you have patients able to tolerate this regimen.[6-8] Total-body irradiation (TBI)[9,10] has also long been a back-bone to myeloablative condition regimens, often given with either cyclophosphamide[11-16] or etoposide[17,18]; pending disease, patient age, and co-morbidity index this could also be considered. Lastly, there are emerging data with alternative nucleoside analogues and busulfan, which may serve as a myeloablative alternative either completely replacing fludarabine or using lower dose fludarabine in combination with an additional purine analogue (i.e., clofarabine or cladribine) to help conserve supply. Those studies are summarized below in Table 1.

Table 1: Myeloablative Conditioning Regimens

Regimen and Reference	Donor	Indication	GVHD Prophylaxis	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations
Flu/Clo/Bu vs Flu/Bu[19] Andersson BS, et al. *Bone Marrow Transplant.* 2022	MSD MUD	AML MDS	Tacrolimus + mini-MTX rATG for MUD	Phase III N=150 Age: 8-70 yrs	Primary-PFS 3 yr PFS 52% vs. 48% Flu/Clo/Bu pts >60 yrs not in CR	Low-dose Flu=10 mg/m2 + Clo 30 mg/m2 Bu given after Flu/Clo with Bu PK*

					had lower relapse incidence (10% vs. 56%, p=0.003)	AEs similar between both arms Additional Flu/Clo/Bu publicatons[20,21]
Clo/Bu[22] Kebriaei P, et al. *Biol Blood Marrow Transplant*. 2017	8/8 MSD or MUD	ALL	Tacrolimus + mini-MTX rATG for MUD	Phase II, single arm, single institution N=107 Age: 19-64 yrs	Primary-Safety and OS 2 yr OS 70%, 57%, and 35% for pts in CR1, CR2, advanced dz (respectively) Favorable safety profile	Bu given after Clo with Bu PK* Additional Clo/Bu publication[23]
Bu4Clo[24] Magenau J, et al. *Bone Marrow Transplant.* 2017	8/8 MSD or MUD	AML	Calcineurin inhibitor + MTX or MMF (no ATG)	Single arm; Multicenter N=71 Age: 19-65 yrs	Primary-EFS at 1 year EFS=20%	*Clo given after Bu and with Bu PK*
Abstracts of Interest						
Gem/Bu/Clo +/- R[25] Nieto Y, et al. Blood. 2017. ASH Abstract. 1966	8/8 MSD or MUD	Aggressive lymphoma	Tacrolimus + MMF rATG for MUD	Phase II dose finding, single center N=48 Age: 12-65 yrs	Dose finding	*Bu given after Gem and Clo infusions and with Bu PK*
Bu/Flu/Clad[26]	8/8-MSD or MUD	AML MDS	FK/MTX vs. PTCy Day +3/4 Tacrolimus +	Phase II N=82	Compared GVHD prophylaxis	Low-dose Flu=10 mg/m2 + Clad 10 mg/m2

Popat U, et al. *Blood.* 2021. ASH Abstract 1803			MMF	Age: 18-70 yrs		*Bu given after Flu/Clad and with Bu PK fractionated*
Bu/Flu/Clad/Ven[27] Popat U, et al. *Blood.* 2021. ASH Abstract 2879	8/8-MSD or MUD	AML MDS	PTCy Day +3/4 Tacrolimus + MMF	Phase II N=33 Age: 18-70 yrs	Preliminary safety and efficacy results	Low-dose Flu=10 mg/m2 + Clad 10 mg/m2 *Bu given after Flu/Clad and with Bu PK fractionated*

*Although studied in a different order, it is recommended that purine nucleoside analogues be given prior to Busulfan due to synergy. Additionally, if able, it is recommended to complete pharmacokinetics with busulfan.

Abbreviations: Bu-busulfan; Cy-cyclophosphamide; Flu-fludarabine; PK-pharmacokinetics; MAC-myeloablative conditioning; MSD-matched sibling/related donor; MUD-matched unrelated donor; 1AgMM-one antigen mismatch; CML-chronic myeloid leukemia; MDS-myelodysplastic syndrome; MPN-myeloproliferative neoplasm; CsA-cyclosporine A; MTX-methotrexate; AML-acute myeloid leukemia; rATG- rabbit antithymocyte globulin; Clo-clofarabine; PFS-progression free survival; OS-overall survival; EFS-event free survival

2) What reduced intensity and non-myeloablative regimens are available for matched donor transplants (sibling or unrelated)?

The advent of reduced intensity (RIC) and non-myeloablative (NMA) conditioning regimens has increased access to HCT for patients previously excluded from myeloablative regimens. Critical to the success of non-myeloablative regimens is adequate immunosuppression without the need for traditional high doses of myeloablative chemotherapeutics. Historically, fludarabine has been utilized as a backbone agent in RIC and NMA regimens to achieve such aims. Fludarabine had become the predominate purine analogue agent incorporated into popular RIC/NMA regimens, such as FluBu2, FluMel, FluCyTBI, etc.

Clofarabine is an alternative purine analogue which has been investigated for non-myeloablative regimens. Two trials enrolling approximately 30-40 patients each were identified. Two studies used clofarabine in combination with busulfan and one included low dose TBI. Clofarabine was evaluated predominately in patients with AML, MDS, and ALL. The engraftment and efficacy date between trials was relatively similar. The decrease in acute graft-versus-host disease (aGVHD) rates seen in the trial by El-Jawahri A. et al. may be due to the use of traditional GVHD

prophylaxis regimen of methotrexate plus a calcineurin inhibitor, compared to the use of rabbit ATG plus a calcineurin inhibitor as utilized by Chevallier P et al. Krakow et al. noted higher rates of especially grade 2 aGVHD and over half of the non-relapse deaths were GVH-related. They do note that non-relapse mortality (NRM) and GVHD did not appear significantly different than a limited analysis compared to historical controls. Grade 3/4 non-hematological toxicities were reported in greater than a third of patients in the study by El-Jawahri A. et al. The authors did recommend avoiding a clofarabine-based conditioning regimen in patients with MDS due to the observed increase in NRM. This may have reflected the older age and baseline comorbidities seen in the MDS population, resulting in less tolerability of clofarabine.

Cladribine is another purine analogue which has been investigated as a fludarabine alternative in non-myeloablative conditioning regimens. In two trials, the cladribine arms were closed early due to inferiority. In the study Giralt S, et al. the Clad/Mel arm was discontinued due to excessive NRM associated with the regimen. In the trial by Markova M, et al., the Clad/Bu/TBI arm was closed due to inferiority compared to the fludarabine arm. Finally, the third trial was a Phase I/II dosing finding study with thiotepa in addition to cladribine and rabbit ATG. The identified safe dose of thiotepa was 133 mg/m^2/day after two patients experienced fatal pulmonary toxicity in phase I. Due to the limited number of patients in this trial, results should be interpreted with caution.

Finally, pentostatin is an additional purine analogue with an alternative mechanism of action compared to the aforementioned medications. Two trials were identified in which pentostatin was used in combination with photopheresis and TBI. Both trials are best classified as phase II trial investigations with limited patient populations, which found relatively high engraftment rates and similar efficacy outcomes. Compared with the other trials using alterative purine analogues, the toxicity profile and rates of GVHD control were improved. The readers should note both trials employed a triplet GVHD prophylaxis approach with cyclosporine, methotrexate and MMF. Kharfan-Dabaja et al. included pentostatin both in “preconditioning” for lymphodepleting effects and combined with busulfan prior to HCT. Pentostatin preconditioning started day –28 and authors interestingly noted a plateau effect after doses of 4 mg/m^2 resulting in ~60% reduction in CD4 and CD8 T-cell counts after 2 weekly doses. The trial also used a relatively high daily target AUC of busulfan at 8000 µmol*min/L/day over 2 days (16000 µmol*min/L total). The trial by Gvajaia A, et al. was an abstract recently published at the American Society of Hematology Annual Meeting detailing an institutional experience using pentostatin + TBI in four patients following previous graft failure. GVHD prophylaxis varied greatly and real-world application is difficult.

There is currently a paucity of data to support any specific alternative purine analogue over traditional fludarabine-based regimens. Based on the studies, clinicians may be advised to avoid cladribine-containing condition regimens due to lack of efficacy data and concern for excessive toxicity. Clorafabine or pentostatin may be alternative regimens, but caution should be warranted given the lack of robust clinical trials. Careful discussion, literature review, and individual patient factors will inevitably factor heavily in ultimate non-fludarabine based regimen selection for RIC transplants.

Table 2: Reduced Intensity and Non-myeloablative Conditioning Regimens

Regimen and Reference	Donor	Indication	GVHD Prophylaxis	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations
CloB2A2[28] Chevallier P, et al. *Haematologica*. 2014	MRD MUD	AML MDS ALL	CsA All pts got rATG	Phase II, multicenter N=30 Age: 20-65 yrs	ANC Engraft: 18d (14-26) PLT Engraft: 12d (0-18) 2yr OS: 58% 2yr LFS: 53% 2yr Relapse: 43% 2yr NRM: 3.3% aGVHD: 40% 2yr cGVHD: 51%	-Limited toxicity data reported -Myeloid disease efficacy outcomes slightly improved vs lymphoid
Clo/Bu[29] El-Jawahri A, et al. *Biol Blood Marrow Transplant.* 2016	8/8 MRD MUD	AML MDS ALL	Tacrolimus + mini-MTX (no ATG)	Phase II N=34 Age: 25-74 yrs	ANC Engraft: 11d (6-17) PLT Engraft: 13d (8-16) 2yr OS: 56% 1yr NRM: 24% 2yr Relapse: 26% aGVHD: 21% aGVHD Gr 3/4: 12% cGVHD: 44% Gr 3/4 Toxicities: 41% Bacterial Infection: 29% Liver: 9%	*Bu given 12hrs after Clo infusion and no Bu PK * -Increase NRM in MDS (all >65yrs & HCT-CI score >4); authors recommend avoid regimen MDS
Clo/TBI[30] Krakow EF et al. *Am J Hematol*. 2020	MUD (80%) MRD (18%) MMUD (2%)	AML	CsA + MMF	Phase I (N=9) Phase II (N=35) Age: 53-74 yrs	All patients engrafted 61% full donor by day 28 OS: 55% 2yr LFS: 52%	-No DLTs in Phase I; Clo 50 mg/m2 days –6 to –2 with 2 Gy TBI day –1

					2yr Relapse: 22% 2yr NRM: 28% aGVHD Gr 2-4: 65% aGVHD Gr 3/4: 9% 2yr cGVHD: 49%	used for Phase II dose -8 of 15 patients with NRM were GVH-related
Clad/Mel[31] Giralt S, et al. *Blood.* 2001	MRD MUD *1AgMM allowed*	Hematologic malignancies	Tacrolimus Mini-MTX	Phase II N=8 (Clad arm) Clad arm closed due to inferiority	D+100 NRM: 87.5% Grade 3/4 Toxicity: Renal: 62.5%	Negative outcome with Clad -Pts previously received Flu were given Clad
Clad/Bu/TBI[32] Markova M, et al. *Bone Marrow Transplant.* 2007	MRD MUD	Hematologic malignancies	CsA and MMF	Prospective, randomized N=16 (Clad arm) Age: 26-60 yrs Clad arm closed due to inferiority of engraftment compared to Flu	ANC Engraft: 12d (10-16) Engraft: 24d (14-23) D+180 NRM: 38% 3yr OS: 25% 3yr Relapse: 28% aGVHD: 69%	Oral Bu, no PK* -Mainly nHL and MM patient population Note: negative outcome with Clad
Clad/Thio/rATG[33] Larsen JT, et al. *Leuk Lymphoma.* 2013	MRD	High-risk hematologic malignances	CsA	Phase I/II (dose finding for Thio) N=12 Age: 26-63 yrs	Phase I (n =2) -Phase I DLT was fatal pulmonary toxicity -New phase II TT Dose: 133mg/m^2/day Phase II (n= 10) ANC Engraft: 17d (10-36) PLT Engraft: 20d (11-37)	-30% of Phase II pts still alive 10 yrs after HCT -Authors caution use in myeloma due

					mOS: 42mo 3yr OS: 60% 1yr NRM: 20% aGVHD: 40% aGVHD 3/4: 10% cGVHD: 30% No Gr4 Non-Hem Toxicity Gr3 Hepatic Toxicity 10%	to increased graft rejections
Pento/Photopheresis/TBI[34] Chan GW, et al. *Biol Blood Marrow Transplant.* 2003	MRD *1AgMM allowed* MUD	MDS	CsA + MTX + MMF	Phase II N=18 Age: 30-70 yrs	Full Chimerism: 89% ANC Engraft: 15d (9-40) Plt Engraft: 20d (8-59) 1yr OS: 65% 1yr TRM: 14% aGVHD Gr 0/1: 81% aGVHD Gr 3/4: 16.6% cGVHD: 47% No Gr 3/4 non-hem tox	Pentostatin CIVI -Lower GVHD and better 1yr OS w/ MDS 6/6 MRD grafts
Pento/Photopheresis/TBI[35] Miller KB, et al. *Bone Marrow Transplant.* 2004	MRD MUD *1AgMM allowed*	Hematologic malignancies	CsA + MTX + MMF	Phase II Two cohorts: Group 1 previous HCT or >3 lines of therapy Group 2 all others N=55 Age: 18-70 yrs	Full Chimerism: 98% 2yr OS: 55% 1yr NRM: 23% Relapse: 7% ANC Engraft: 17d (9-29) PLT Engraft: 20d (0-100) aGVHD: 9% aGVHD 3/4: 4% cGVHD: 43%	Pentostatin CIVI -GVHD MTX was 2 dose series -1yr OS 62% for group 1 vs 71% for group 2 (p=0.05)

					Alopecia: 100% AKI: 25% Facial Erythema: 37%	
Pento/Bu[36] Kharfan-Dabaja M et al. *Biol Blood Marrow Transplant*. 2013	7/8 or 8/8 MSD or MUD	Hematologic malignancies Plurality CLL (45%)	Tac + MTX or Tac + siro	Phase II N=42 Age: 29-73 yrs	Full Chimerism: 87% by day +28, 96% day +100 2yr OS: 68% 2 yr Progression: 30% 2yr NRM: 17% aGVHD Gr 2-4: 59% aGVHD Gr 3/4: 19% cGVHD: 69%	-Busulfan given days –4 and –2 with AUC cumulative target of 16000 umol*min/L -See pentostatin discussion above
Pento/TBI[37] Gvajaia A, et al. *Blood*. 2019. ASH Abstract 5657	MRD MUD	Not reported	Misc. per provider: Tacrolimus + MTX Tacrolimus + MMF PTCy + MMF + Sirolimus PTCy + MMF + Tacrolimus	N=4 Age: 23-51 All previous graft failure (2 primary & 2 secondary)	Full Chimerism: 100% ANC Engraft: 22d PLT Engraft: 54d Avg Hospitalization: 39d Median 3.5yr follow-up 3/4 patients still alive No episodes of aGVHD or cGVHD No VOD, Gr 3/4 mucositis, enteritis, or pulmonary toxicity 1 death due to infection	-GVHD prophy variable per patient (PTCy and MTX based) -One patient received 2 previous transplants

*Although studied in a different order, it is recommended that purine nucleoside analogues be given prior to Busulfan due to synergy. Additionally, if able it is recommended to complete pharmacokinetics with busulfan.

Clad-cladribine; Mel-melphalan; RIC-reduced intensity conditioning; MRD-matched related donor; MUD-matched unrelated donor; 1AgMM-one antigen mismatch; Bu-Busulfan; PK-pharmacokinetics; MTX-methotrexate; MM-multiple myeloma; CsA-cyclosporine; MMF -mycophenolate mofetil; Thio-thiotepa; rATG-rabbit antithymocyte globulin

3) What conditioning regimens are available for alternative donor transplants (haploidentical and cords)?

Alternative donor transplants have expanded our reach to patients that may have otherwise been unable to receive a transplant if they did not have a matched sibling or unrelated donor available. Fludarabine has frequently been used to help provide adequate immunosuppression to decrease the risk of graft failure. Limited data are available in haploidentical and cord transplants using alternative regimens.

Table 3: Conditioning Regimens for Haploidentical or Cord Transplants

Regimen and Reference	Donor	Indication	GVHD Prophylaxis	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations
Clo-Baltimore[38] (Cy/Clo/TBI) Chevallier P, et al. *Oncotarget*. 2018	Haplo (75%) MSD (17%) MUD (6%) MMUD (2%) PBSC graft (100%)	AML MDS MF CML/MPN BPDCN	PTCy + CsA + MMF	Retrospective N=36 Age: 31-70 yrs	ANC engraftment 100%, median 18 days (8-27 days) Platelet recovery 100%, median 28.5 days (11-111 days) aGVHD (Grade 2-4): 49%; aGVHD (Grade 3-4): 9%	Incidence of aGVHD was high, likely due to PBSC source

					cGVHD 21% NRM: 100 days 5.5% 2 yr GFRS: 41% 2 yr OS: 66%	
Clo/Bu4[39] Takagi M, et al. *Int J Hematol*. 2017	Haplo (100%) BM graft (100%)	ALL NK/T-cell leukemia	rATG + Tacrolimus + MTX + steroids	Case series N=3 Age: 6-12 yrs Third HCT for 66% of patients	ANC engraftment 100%, median 19 days (16-22 days) Platelet recovery 100%, median 34 days (22-50 days) aGVHD (Grade 1-2): 66%; aGVHD (Grade 3-4): 0% cGVHD 33% OS: 100% (Case 1: 167 weeks, Case 2: 49 weeks, Case 3: 31 weeks)	Limited case report Short observation period for disease response and cGVHD evaluations
Pento/Cy/Bu[40] Dimitrova D, et al. *Biol Blood Marrow Transplant.* 2020	Haplo (35%) MUD (40%) MSD (25%)	Primary immuno-deficiency	PTCy + Sirolimus + MMF	Single-center, prospective trial N=20 Age: 4-58 yrs	ANC engraftment 100%, median 17 days (14-42 days)	Both patients with graft failure received haplo grafts, however the 5 other haplo

	T-cell replete BM graft (100%)				Platelet recovery 100%, median 30 days (16-45 days) aGVHD (Grade 2-4): 15%; aGVHD (Grade 3-4): 5% cGVHD: 0% 5% experienced SOS Day +180 GGFS: 80% Graft Failure: 10% 1 yr OS: 90%	grafts included in this study had outcomes similar to recipients of matched grafts. Graft failure thought to be likely related to underlying disease features and disease activity in the periengraftment period.
Clo/Thio/Mel[41] Boulad, et al. *Blood.* 2012	dCBT (23%) *T-cell replete BM/PBSCT* MRD (17%) MMRD (2%) MUD (19%) MMUD (4%) *T-cell deplete stem cells* MRD (13%)	ALL AML MDS	*dCBT* Tacrolimus + MMF	N=64 *dCBT Arm:* N=15 Age: 0.9-58 yrs **combined age for dCBT and T-cell replete BM/PBSCT arms*	Engraftment occurred in 56/61 evaluable patients dCBT Arm: aGVHD (Grade 2-4): 38% 20.5 mo DFS: 41.5%	Time to engraftment not provided

	MMRD (2%) MUD (6%) MMUD (14%)				20.5 mo OS: 51.3%	
Cy/TBI/Ara-C[42] Takahashi S, et al. *Blood*. 2004	CBT (60%) MUD (40%) *1AgMM allowed*	AML ALL CML MDS NHL	CsA + MTX	Retrospective N=113 CBT Arm: N=68 Age: 16-53 yrs	CBT Arm: ANC engraftment 88%, median 22 days (16-41 days) Platelet recovery 81%, median 40 days (13-99 days) aGVHD (Grade 2-4): 50%; aGVHD (Grade 3-4): 7% cGVHD: 78% 2 yr incidence of relapse: 16% 1 yr TRM: 9% 2 yr DFS: 74%	

Abbreviations: 1AgMM-one antigen mismatch; AE-adverse event; ALL-refractory acute lymphoblastic leukemia; AML-acute myeloid leukemia; Ara-C-cytarabine; BM-bone marrow; BPDCN- Blastic plasmacytoid dendritic cell neoplasm; Bu-busulfan; CBT-cord blood transplant; Clo-clofarabine; CML-chronic myeloid leukemia; CsA-cyclosporine A; Cy-cyclophosphamide; dCBT-double unit cord blood transplant; DFS-disease free survival; Flu-fludarabine; GGFS- GVHD-free, graft failure-free survival; GRFS-GVHD-free, relapse-free survival; Haplo-haploidentical; Mel-melphalan; MF-myelofibrosis; MMF-mycophenolate mofetil; MSD-matched sibling/related donor; MUD-matched unrelated donor; MDS-myelodysplastic syndrome; MMRD-mis-matched related donor; MMUD-mis-matched unrelated donor; Mo-month; MPN-myeloproliferative neoplasm; MTX-methotrexate; NHL-non-Hodgkin lymphoma; PBSC-peripheral blood stem cell; PTCy-post-transplant cyclophosphamide; rATG- rabbit antithymocyte globulin; SOS- sinusoidal obstructive syndrome; TBI-total body irradiation; Thio-thiotepa; TRM-transplant related mortality

Section C: Pharmacologic Considerations of Alternate Purine Nucleoside Analogues

1) **What are some pharmacologic considerations when choosing an alternative nucleoside analogue as part of your conditioning regimen?**

Nucleoside analogues other than fludarabine have been used in transplant conditioning regimens. It is important to note that these agents have not been studied or used as extensively as fludarabine and most of the available data is limited to reports of single-center experiences or phase II data. Key pharmacologic characteristics of these alternative agents are listed in the table below to aid in selection in appropriate clinical scenarios.

Table 4: Purine Nucleoside Analogues

Drug	Doses in HCT	Metabolism	Half-life	Elimination	Select Toxicities
Cladribine	5 to 12 mg/m^2/day IV for 4 to 5 days	Activated by phosphorylation to active moiety	IV: 5.4 hours	Urine (18-25%)	Cardiac Hepatic Neurologic Renal
Clofarabine[20,43,44]	30-40 mg/m^2 IV daily for 4 doses (course max of 160 mg/m^2)	Intracellularly to active metabolite	Age 2 to 19 yrs: 5.2 hrs Children/adults: 7 hrs May be prolonged in elderly and renal impairment	Urine (49-60% as unchanged drug)	Hepatic Dermatologic Capillary leak syndrome Gastrointestinal Renal
Fludarabine[45-47]	25-40 mg/m^2 IV daily for 3-5 days (course max of 200 mg/m^2)	Dephosphorylated then phosphorylated to active metabolite	2-fluoro-ara-A: 20 hours	Urine (60% as dephosphorylated metabolite)	Neurologic Pulmonary
Pentostatin	4 mg/m^2/day IV continuous infusion daily for 2 days 4 mg/m^2 IV as a single dose	Minimal	5.7 hrs CrCl < 50 ml/min – 11 to 23 hours	Urine (90%)	Pulmonary Renal Neurologic Dermatologic Hepatic

Section D: Lymphodepletion for CAR T-cell Recipients

1) Are there any studies using another lymphodepletion strategy aside from Fludarabine/Cyclophosphamide for CAR-T cell therapy?

Early CAR-T studies have demonstrated the benefit of adding fludarabine to cyclophosphamide alone with improved expansion and persistence of CAR T-cells as well as improved response rates.[48,49] All of the commercially available CAR-T products recommend this FluCy backbone as the preferred regimen for lymphodepletion. Only tisagenlecleucel describes an alternative option with bendamustine monotherapy for patients with a history of hemorrhagic cystitis or previously documented cyclophosphamide resistance. Both the initial experience and recently published papers have suggested the substitution to bendamustine in lieu of fludarabine availability may be appropriate for patients receiving tisagenlecleucel. The follow up from the Juliet study published in 2021 reported a numeric decrease in the 24-month progression-free survival (PFS) with bendamustine lymphodepletion.[3] However, this observation is tied to and biased by patient selection and was also a post-hoc evaluation that was not statistically evaluated. Recently a multicenter retrospective study from two US and one European center evaluated bendamustine vs FluCy in patients receiving tisagenlecleucel.[4] Regimens were selected based on physician preference. The study found that bendamustine alone compared favorably to the FluCy regimen with similar overall response rate (ORR) and PFS with reduced CAR-T-related toxicity (cytopenias, neutropenic fever, cytokine release syndrome, infection, hospital utilization, etc). The authors appropriately discuss the limitations of the retrospective paper but these data provide some encouraging signals for safe alternatives in the setting of the ongoing, dire fludarabine shortage.

Although extrapolation to other CAR-T products is a seemingly reasonable approach, other studies have suggested that fludarabine is an essential component in lymphodepletion. A phase I/II trial of a CD30 target CAR-T therapy with a similar 4-1bb costimulatory domain found fludarabine was essential to CAR-T expansion and persistence that corresponded to ORR.[5] The ability to draw conclusions from the study are limited by the specific patient population, target of the CAR-T therapy, and the small number of patients who received bendamustine alone. However, these data highlight the real concern that using alternative lymphodepleting regimens with products other than tisagenlecleucel may have unexpected impacts on the success of the CAR-T therapy.

Unfortunately, limited data is available to recommend widespread adoption of alternative regimens. Centers must closely evaluate the existing data and current fludarabine availability to carefully determine if/when changing lymphodepletion regimens to bendamustine might be appropriate.

Table 5: Lymphodepletion for CART

Lymphodepletion and Reference	CART Type	Indication	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations

FluCy Bendamustine[3] Schuster SJ, et al. Lancet Oncol. 2021	Anti-CD19 CAR-T (tisagenlecleucel)	Large B-cell Lymphomas	Phase II, multicenter, open-label FluCy: N=85 Benda: N=22	ORR: 61% - not reported by LD regimen	24-month PFS numerically lower with bendamustine; possibly biased by other patient factors
FluCy Bendamustine[4] Ghilardi G, et al. *Ann Oncol.* 2022	Anti-CD19 CAR-T (tisagenlecleucel)	Large B-cell Lymphomas	Retrospective, multicenter FluCy: N=42 Benda: N=90	ORR: 42.9% vs 50% (FluCy vs Benda; p=0.444)	CAR-T-related AEs reported significantly lower with bendamustine
FluCy FluBenda Bendamustine[5] Ramos CA, et al. *J Clin Oncol.* 2020	Anti-CD30 CAR-T (investigational)	Hodgkin Lymphoma	Phase I/II, multicenter, open-label FluCy: N=17 FluBenda: N=15 Benda: N=5	ORR: 63% - FluCy: 65% - FluBenda: 80% - Benda: 0%	Fludarabine treated patients had significantly higher IL-7, IL-15, and CAR-T persistence

Flu-fludarabine; Cy-cyclophosphamide; Benda-Bendamustine; ORR-overall response rate; LD-lymphodepletion

Section E: Pediatric Considerations.

1) **What are some pediatric considerations when selecting alterative fludarabine based preparative regimens?**

For pediatric leukemias busulfan/cyclophosphamide, cyclophosphamide/TBI regimens continue to be the classical conditioning regimens for pediatric patients undergoing first HCT.

Transplant for non-malignant indications

Advances in allogeneic HCT for non-malignant indications have largely been based on non-myeloablative, reduced intensity, and reduced toxicity myeloablative regimens that include fludarabine. Patients with a non-malignant indication for transplant for whom a fludarabine based conditioning regimen is preferred should be evaluated for ability to delay transplantation until fludarabine stock is replenished. If transplant is unable to be delayed, considerations for substituting with a clofarabine based regimen, using an alternative regimen or a myeloablative regimen should be considered on a case-by-case basis. There are no extensive data on which to base decisions regarding clofarabine based preparative

regimens in pediatric non-malignant diseases. In situations where there are historic data using a myeloablative regimen in a particular disease state, the change in NRM associated with using a myeloablative regimen should be considered when selecting an approach

Table 6: Additional Myeloablative Regimens for Pediatric Leukemia

Regimen and Reference	Donor	Indication	GVHD Prophylaxis	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations
Clo/Mel/TT[50] Spitzer B, et al. *Biol Blood Marrow Transplant*. 2016	Same as previous donor (N=13) New MUD (N=1) New MMU (N=3)	2nd or 3rd transplant for high risk ALL or AML	T cell depletion, tacrolimus + MMF or MTX	Single center retrospective review	3 year disease free survival 50%	

Clo-Clofarabine; Mel-Melphalan; TT-Thiotepa; MUD-matched unrelated donor MMU- mismatched cord ; ALL-acute lymphoblastic leukemia; AML-acute myeloid leukemia; MMF-mycophenolate mofetil; MTX-methotrexate

Section F: PO Fludarabine

1) Is Fludarabine only available as IV?

Fludarabine phosphate as an oral formulation has been available in the several countries outside of the Unites States (U.S.) since 2001. In the U.S. it was approved by the U.S. Food and Drug Administration (FDA) in 2008 under accelerated approval for the treatment of relapsed CLL, but in 2011 was withdrawn from the market in the United States due to challenges in completing a post-marketing study required by the FDA which occurred because of to lack of commercial demand.

Fludarabine phosphate is available in other countries as follows but can only be used in the United States if the FDA grants emergency import of the product. As of now, this has not occurred.

- Australia – 10 mg tablets - Sanofi-Aventis Australia
- Canada – 10 mg tablets - Sanofi-Aventis Canada
- Europe (several countries) - 10 mg tablets – Genzyme Europe BV
- United Kingdom – 10 mg tablets – Genzyme Europe BV

Oral fludarabine phosphate in immediate release tablet formulation is approximately 55% bioavailable (range of 30 to 80%). Studies looking at pharmacokinetic properties demonstrated that a once daily dose of 40 mg/m^2 of immediate release PO formulation (independent of food intake) provides similar systemic exposure compared to 25 mg/m^2 IV (making the PO dose is 1.6 times higher than the IV dose). Adverse reactions are similar between IV and PO formulation with regard to myelosuppression and infectious complications, however gastrointestinal adverse effects are more common with the PO formulation. Grade 1 to 2 and grade 3 to 4 nausea/vomiting was reported to be ~37 to 38% and 1.2 to 1.3 % respectively, and grade 1 to 2 and grade 3 to 4 diarrhea was 34 to 42% and 3.8 to 6.4% respectively.

Table 7: PO Fludarabine Regimens

Regimen and Reference	Donor	Indication	GVHD Prophylaxis	Characteristics	Primary Endpoint and Notable Secondary Endpoints	Considerations
PO or IV Flu/Mel or PO Flu/Bu[51] Delgado J, et al. *Cytotherapy*. 2009	MRD MUD *1AgMM allowed*	Hematologic malignancies	MSD: CsA + MTX/leucovorin MUD: CsA + MMF rATG added for 1AgMM	Non-randomized, retrospective N=37 PO Flu N=144 IV Flu Age (PO arm): 21-69 yrs	Engraftment, hospital LOS, GVHD, NRM	8% of patients in PO arm changed to IV due to GI toxicity Substitution of 30 mg/m^2 with 48 mg/m^2 in RIC
PO or IV Flu/PO Bu/IV Cy[52] Velazquez-Sanchez-de-Cima S, et al. *Acta Haematol.* 2014	MRD	Hematologic malignancies	CsA + mini-MTX	Non-randomized, retrospective N=55 PO Flu N=113 IV Flu Age (PO arm): 9-70 yrs	Engraftment, NRM, OS, GVHD	Substitution of 30 mg/m^2 with 35 mg/m^2 in RIC
PO Flu/Mel+/-TBI[53]	MRD MUD *1AgMM allowed*	Hematologic malignancies	CsA + MTX +/- ATG +/- prednisolone	Non-randomized, retrospective N=104 Age: 26-70 yrs	Engraftment, GVHD, OS, DFS survival compared to historical data	Substitution of 25 mg/m^2 with 40 mg/m^2 in RIC

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Abbreviations: Flu-fludarabine; Mel-melphalan; Bu-busulfan; MSD-matched sibling/related donor; MUD-matched unrelated donor; 1AgMM-one antigen mismatch; CsA-cyclosporine A; MTX-methotrexate; rATG- rabbit antithymocyte globulin; LOS-length of stay; GVHD-graft versus host disease; NRM-non relapse mortality; GI-gastrointestinal; RIC-reduced intensity conditioning; Cy-cyclophosphamide; OS-overall survival; TBI-total body irradiation; DFS-disease free survival

Summary

The national fludarabine shortage has presented many challenges to clinical practitioners as supply remains low and some centers are unable to purchase additional supply. As a result, those centers that still have some supply can utilize various strategies to conserve fludarabine use, which include dose rounding, batching doses, minimizing its use outside of HCT/CAR-T therapy, consolidating supplies, and extended beyond use dating. For centers who are unable to obtain supply and those who will not have sufficient supply for upcoming patients, this FAQ provides a summary of the available data for alternative conditioning and lymphodepleting regimens along with references to assist providers with the current available evidence if choosing an alternative regimen is needed.

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