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Capt. Valerie Jensen, RPh
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Dear Dr. Cavazzoni and Capt. Jensen:

On behalf of the American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match/ National Marrow Donor Program (NMDP) our organizations write to address the recent fludarabine shortage experienced by centers nationwide. ASTCT's Pharmacy Special Interest Group has help prepare this letter to emphasize the impact the shortage has had on their facilities and lack of evidence-based medicine to aid in mitigation strategies.

The ongoing shortage has significant, direct patient impact that is of utmost concern to the transplant and cellular therapy community. Stem cell transplant (SCT) and chimeric antigen receptor T-cell (CAR-T) therapies are the only curative option for many malignancies and are used to treat thousands of patients per year[1] with demand rapidly increasing as new cellular therapy agents continue to gain FDA-approval. Fludarabine administration is a critical component of these therapies that is commonly used in both SCT conditioning and CAR-T lymphodepletion. These therapies are time sensitive in the setting of high risk malignancies that do not allow for therapy delays based on drug shortages. The uncertainty or unavailability of supply has led centers to begin rationing treatments or changing to inferior, more toxic alternatives directly impacting patient care.

The ASTCT is a professional membership association of more than 3,000 physicians, scientists, pharmacists, and other health care professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication, and clinical standards. Our Society's clinical teams have been instrumental in developing and implementing clinical care standards and advancing cellular therapy science, including participation in trials that led to current FDA approvals for chimeric antigen receptor T-cell (CAR-T) therapy.

The NMDP operates the Congressionally authorized program that matches unrelated volunteer donors with patients in the United States and abroad who have been diagnosed with leukemia as well as over 75 more otherwise fatal blood cancers, disorders, and diseases. Under contract with the Department of Health and Human Services/Health Resources & Services Administration, the program has for over 30 years been charged with providing equal access for all patients in a need of a life-saving transplant. As the steward of this critical federal public health program, we partner with 155 domestic hospital transplant programs in assisting them with efforts to provide access to transplant.

Within transplant conditioning, fludarabine-based regimens have been extensively used and are considered a standard. The shortage has led centers to move away from these standard treatment regimens to non-fludarabine based alternatives that are known to be more toxic or have limited data supporting their use. For example, the most common conditioning regimen for acute myeloid leukemia or myelodysplastic syndrome over the last 10 years has been busulfan plus fludarabine.[1] The shortage has forced centers to use an older regimen consisting of busulfan plus cyclophosphamide (BuCy) despite ample evidence within these 10 years indicating increased toxicity with BuCy.[2,3] Other alternatives such as total body irradiation-based regimens also have notably increased toxicity when compared to fludarabine-based therapy.[4] Nearly all of the reduced intensity conditioning regimens that are currently used in practice also contain a fludarabine backbone for its immunosuppressive effects.

Transplant centers have also been forced to move away from fludarabine-based regimens and use alternative drugs such as cladribine or clofarabine which are both significantly less studied and rely on single-center experience or limited Phase II data. The continued increasing use of haploidentical and umbilical cord blood (UCB) transplants has led to expanded access to lifesaving modalities within minority communities that are often underrepresented in donor registries.[1] All of the standard haploidentical and UCB conditioning regimens contain fludarabine and switching to these under validated regimens may have significant impacts for these, often minority, patient population. The limited availability of fludarabine is leading to the use of alternative regimens that are known to be more toxic or under studied alternatives with unknown long-term clinical effects or harms to patients.

CAR-T lymphodepletion also extensively relies on fludarabine. Only one FDA-approved product lists bendamustine as an alternative to fludarabine plus cyclophosphamide lymphodepletion in the labeling and there is limited data to support its use outside of tisagenlecleucel (Kymriah). There is continued emerging data that fludarabine-based lymphodepletion is critical for T-cell persistence and the ultimate efficacy of the T-cell product.[5] This substitution to bendamustine must not be widely accepted and may have serious effects in term of efficacy in this patient population. **This continued fludarabine shortage is forcing centers to use non-FDA approved lymphodepleting regimens that may negatively impact the success of a possibly lifesaving CAR-T therapy**.

We request the FDA to take immediate action on this critical shortage. Many centers currently have no ability to purchase fludarabine through their suppliers and have no estimated time frame for return of availability. Other centers are limited to mere weeks of supply with continued uncertainty of future availability.

Outside of the US, oral fludarabine is an available, marketed agent that might be an appropriate alternative if made available in the US. The European Medicines Agency, [6,7] the Canadian Drug and Health Product Register, [8,9] and the Therapeutic Good Administration in Australia, [10,11] appear to have both fludarabine tablets and IV fludarabine approved and are not reporting a similar drug shortage. The shortage was likely exacerbated by the closure of a pharmaceutical manufacturing facility. Future regulation for industry-based

shortage mitigation strategies prior to halting drug production may reduce the likelihood of shortage-related patient harm.

Institutions have already been forced to develop algorithms for limiting use and rationing supply due to this shortage. Additionally, our physicians and institutions are already working with legal and ethical teams to determine who should receive essential, standard of care, lifesaving chemotherapy and who will be delayed. Institutions are being forced to alter treatment plans to more toxic or less effective regimens. Therefore, patients are already experiencing the significant impact of this ongoing shortage.

Our organizations thank the FDA for their prompt response to this shortage and appreciate the opportunity to weigh in on behalf of our patient population. If you have any additional questions please contact Alycia Maloney, Director of Government Relations for ASTCT, at amaloney@astct.org or ASTCT's Pharmacy Special Interest Group Chair, Ryan Shaw, PharmD, at Ryan.Shaw@unchealth.unc.edu.

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Research

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