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Hypoxia-specific imaging in patients with lymphoma undergoing CAR-T therapy

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Abstract

Purpose—Intratumoral hypoxia in non-Hodgkin's Lymphoma (NHL) may interfere with chimeric antigen receptor T-cell (CAR-T) function. We conducted a single-center pilot study (clinicaltrials.gov ID NCT04409314) of [18F]fluoroazomycin arabinoside, a hypoxia-specific radiotracer abbreviated as [18F]FAZA, to assess the feasibility of this positron emission tomography (PET) imaging modality in this population.

Methods—Patients with relapsed NHL being evaluated for CAR-T therapy received a one-time [18F]FAZA PET scan before pre-CAR-T lymphodepletion. A tumor to mediastinum (T/M) ratio of 1.2 or higher with regard to [18F]FAZA uptake was defined as positive for intratumoral hypoxia. We planned to enroll 30 patients with an interim futility analysis after 16 scans.

Results—Of 16 scanned patients, 3 had no evidence of disease by standard [18F]fluorodeoxyglucose PET imaging before CAR-T therapy. Six patients (38%) had any [18F]FAZA uptake above background. Using a T/M cutoff of 1.20, only one patient (a 68-year-old male with relapsed diffuse large B-cell lymphoma) demonstrated intratumoral hypoxia in an extranodal chest wall lesion (T/M 1.35). Interestingly, of all 16 scanned patients, he was the only patient with progressive disease within 1 month of CAR-T therapy. However, because of our low overall proportion of positive scans, our study was stopped for futility.

Conclusions—Our pilot study identified low-level [18F]FAZA uptake in a small number of patients with NHL receiving CAR-T therapy. The only patient who met our pre-specified threshold for intratumoral hypoxia was also the only patient with early CAR-T failure. Future plans include exploration of [18F]FAZA in a more selected patient population.

Keywords

PET; FAZA; CAR-T; Lymphoma; Hypoxia

Introduction

CD19-directed chimeric antigen receptor T-cell (CAR-T) therapies have led to durable complete responses in approximately 30–40% of patients with relapsed non-Hodgkin's lymphoma (NHL) [1, 2]]. However, almost half of CAR-T failures in NHL occur within the first month of infusion [3]. Various tumor-specific mechanisms have been postulated for early CAR-T failure: high tumor bulk, elevated lactate dehydrogenase (LDH), tumor-mediated immune dysregulation, and high baseline levels of systemic inflammation [3–6]. Some of these factors may be associated with hypoxia within the tumor microenvironment, a known driver of lymphomagenesis and aggressive disease biology [7–9]. Intratumoral hypoxia also mediates T-cell dysfunction through upregulation of hypoxia-inducible factor (HIF) 1α, generation of extracellular free adenosine, and prevention of oxidative phosphorylation by CD4 T cells [10–13]. Downstream effects of intratumoral hypoxia include direct T-cell inhibition, decreased effector function, and increased exhaustion. In pre-clinical models, intratumoral hypoxia has been shown to impair effector CAR-T activity as well [14, 15].

Intratumoral hypoxia may thus predict inferior clinical outcomes to CAR-T therapy in lymphoma. [18F]fluoroazomycin arabinoside, abbreviated as [18F]FAZA, is a hypoxia-specific radiotracer that is trapped within cells when the partial pressure of oxygen falls below 10 mm of mercury [16]. Compared to older hypoxia-specific radiotracers like [18F]fluoromisonidazole, [18F]FAZA has favorable biokinetics in terms of hydrophilicity and differential clearance from hypoxic tissues versus blood [17–19]. Compared to HIF 1α immunohistochemical staining from tissue biopsies, [18F]FAZA non-invasively and directly measures hypoxia throughout the entire body. Elevated [18F]FAZA uptake on positron emission tomography (PET) imaging has been associated with worsened outcomes in solid malignancies [20, 21]. However, [18F] FAZA has not yet been studied in the setting of CAR-T therapies for hematologic malignancies.

Materials and methods

We conducted a single-center Phase 1 study of [18F]FAZA in adult patients receiving CD19 CAR-T therapy for NHL (including indolent NHL) to assess its feasibility and safety and secondarily to explore any associations between [18F] FAZA uptake and post-CAR-T outcomes. There were no restrictions on CAR-T product, disease status at the time of [18F]FAZA scan, bridging therapy, or ambulatory pulse oximetry values. Our study was registered at clinicaltrials.gov (NCT04409314) and received approval from the University of California San Francisco Institutional Review Board.

After providing informed consent, enrolled patients received a one-time intravenous dose of 10–25 μg of [18F]FAZA followed by a PET scan 2 h later. The radiotracer was produced at our facility using the same synthesis process described previously [22]. All scans were performed using a fully digital time-of-flight PET scanner with continuous-motion images acquired from vertex to mid-thigh and 2 min per bed position. With regard to timing, [18F]FAZA PET scans were performed at any feasible timepoint between initial evaluation and lymphodepletion. Based on previous work in solid oncology [23, 24], we defined a positive scan as any lymphoma-attributable volume of interest with a tumor to mediastinum (T/M) ratio of 1.20 in terms of maximum standard uptake value (SUV_{max}) versus background uptake in the descending aorta or (for patients with mediastinal disease) unaffected hepatic parenchyma.

Other pertinent data points included the most recent LDH value before [18F]FAZA scan as well as the results of standard of care (SOC) [18F]fluorodeoxyglucose ([18F]FDG) PET imaging both before and after CAR-T therapy. Day + 30 responses to CAR-T therapy were calculated using Lugano 5-point scale (PS) criteria as applied to SOC [18F]FDG imaging. Based on limited data with [18F]FAZA from an early study of multiple types of cancer that included 15 patients with NHL [18], we hypothesized that positive [18F]FAZA scans in 60% of patients would warrant further investigation. Using the Simon two-stage minimax design to reject the null hypothesis (that < 40% would have positive scans) with alpha 0.10 and power 0.80, we planned to enroll 30 patients with an interim futility analysis after 16 scans and study closure for 6 positive scans. The results of this interim analysis are described here.

Results

As shown in Table 1, 16 patients (14 with aggressive B-cell lymphomas, 1 with mantle cell lymphoma, and 1 with follicular lymphoma) underwent [18F]FAZA PET scans between August 2021 and December 2022. Importantly, 3 patients had no evidence of disease on SOC [18F] FDG imaging obtained at roughly similar timeframes to their [18F]FAZA scans before CAR-T therapy. Three patients received bridging chemotherapy after T-cell collection, in two cases before the [18F]FAZA scan and in one case afterward. Two patients did not ultimately receive CAR-T therapy, in one case due to personal preference and in one case due to lymphoma-related death. Of the 14 patients who did receive CAR-T therapy, [18F]FAZA scans occurred a median of 16 days (range 7–70 days) prior to CAR-T infusion.

[^{18}F]FAZA was well tolerated, with only a single episode of Grade 1 nausea in one patient that resolved the following day.

Overall, 6 patients (38% of the cohort) had any [^{18}F] FAZA uptake above background. Using our pre-specified T/M cutoff of 1.20, however, only one patient (Patient 05) demonstrated intratumoral hypoxia. This patient, a 68-year-old male with relapsed diffuse large B-cell lymphoma, had multiple [^{18}F]FDG-avid lesions on pre-CAR-T imaging including an extranodal chest wall mass with a metabolic tumor volume of 3.5 cm^3 (Fig. 1A). Subsequent [^{18}F]FAZA imaging performed 20 days before CAR-T therapy without interceding bridging chemotherapy (Fig. 1B) demonstrated this mass as his only [^{18}F]FAZA-avid lesion with an SUV$_{max}$ of 2.12. [^{18}F]FDG imaging at Day + 30 and Day + 90 after lisocabtagene maraleucel, a CD19-directed CAR-T therapy (Fig. 1C and D), both demonstrated PS5 responses consistent with progressive disease (PD). Of our 16 scanned patients, he was the only patient with PD as the best response to CAR-T therapy. However, because of our low overall proportion of patients with a priori defined positive [^{18}F]FAZA scans, our study was stopped for futility.

Discussion

Our pilot study identified low-level [^{18}F]FAZA uptake in a small number of patients with NHL receiving CAR-T therapy. The only patient who met our pre-specified threshold for intratumoral hypoxia was interestingly also the only patient with early CAR-T failure, with progressive disease noted both at Day + 30 and Day + 90. However, elevated [^{18}F]FAZA uptake was relatively uncommon among patients in our study. Compared to a historical study of [^{18}F]FAZA across cancer types which demonstrated a 40% incidence of intratumoral hypoxia in 15 patients with NHL [18], rates of intratumoral hypoxia in our study were undoubtedly lower despite a comparable distribution of NHL histology. This may reflect differences in patient population given our emphasis on pre-CAR-T imaging, including in patients who had achieved a complete response with antecedent pre-CAR-T bridging therapy. Alternatively, given that at least half of the cases of intratumoral hypoxia in the previous study appeared to involve extranodal disease (similarly noted in our patient with a hypoxic chest wall mass), [^{18}F]FAZA avidity may be disproportionately likely to occur in extranodal deposits.

Limitations of our study include its small sample size and heterogeneous patient population, including many patients who did not require bridging and 3 patients with no evidence of pre-CAR-T disease by SOC imaging. The optimal T/M ratio to identify elevated [^{18}F]FAZA uptake is unclear. Had we used a more liberal threshold of T/M > 1.00, 38% of our scans ($n = 6$, including half of patients with suboptimal responses to CAR-T therapy) would have been classified as positive. Conversely, had we used a T/M threshold of 1.4 as done in some previous studies [20, 23, 25, 26], no patients would have been classified as positive. This raises the question of whether [^{18}F]FAZA uptake may be prognostically useful in a more narrowly defined population of patients with a looser definition of intratumoral hypoxia. This selected population might include patients with extranodal disease as noted above, high metabolic tumor volume, markedly elevated LDH, or previous failure of other CAR-T therapies. Conversely, patients without increased avidity on SOC PET imaging are

unlikely to benefit from [18F]FAZA imaging. Steps to accommodate these changes in a future iteration of our protocol are underway.

If shown in future studies to be a reliable marker of adverse post-CAR-T outcomes in high-risk patients, elevated [18F]FAZA uptake is potentially more actionable than other negative prognostic markers such as high tumor burden. For example, targeted radiation therapy to sites of intratumoral hypoxia may help promote normoxia and ensure tumor control in these areas regardless of T-cell effector function [27, 28]. Alternatively, given that CD28 costimulatory domains within CAR-T constructs confer less dependence on mitochondrial-driven oxidative respiration than do 4-1BB costimulatory domains [29], profound intratumoral hypoxia could theoretically affect the choice of commercially available CAR-T therapy. In our study patient with demonstrated intratumoral hypoxia, for example, he received a CAR-T product with a 4-1BB costimulatory domain. However, these theories are speculative and require further investigation once the prognostic value of [18F]FAZA is validated.

Conclusion

In conclusion, our pilot study of [18F]FAZA PET imaging in NHL did not detect a significant proportion of study-defined hypoxia. The only patient with unequivocal intratumoral hypoxia on [18F]FAZA imaging was also the only patient with early tumor progression following CAR-T therapy. Future studies with [18F]FAZA in a more narrowly defined patient population are planned.

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Competing interests

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Data availability

Data are available upon reasonable request by emailing the corresponding author (rahul.banerjee.md@gmail.com).

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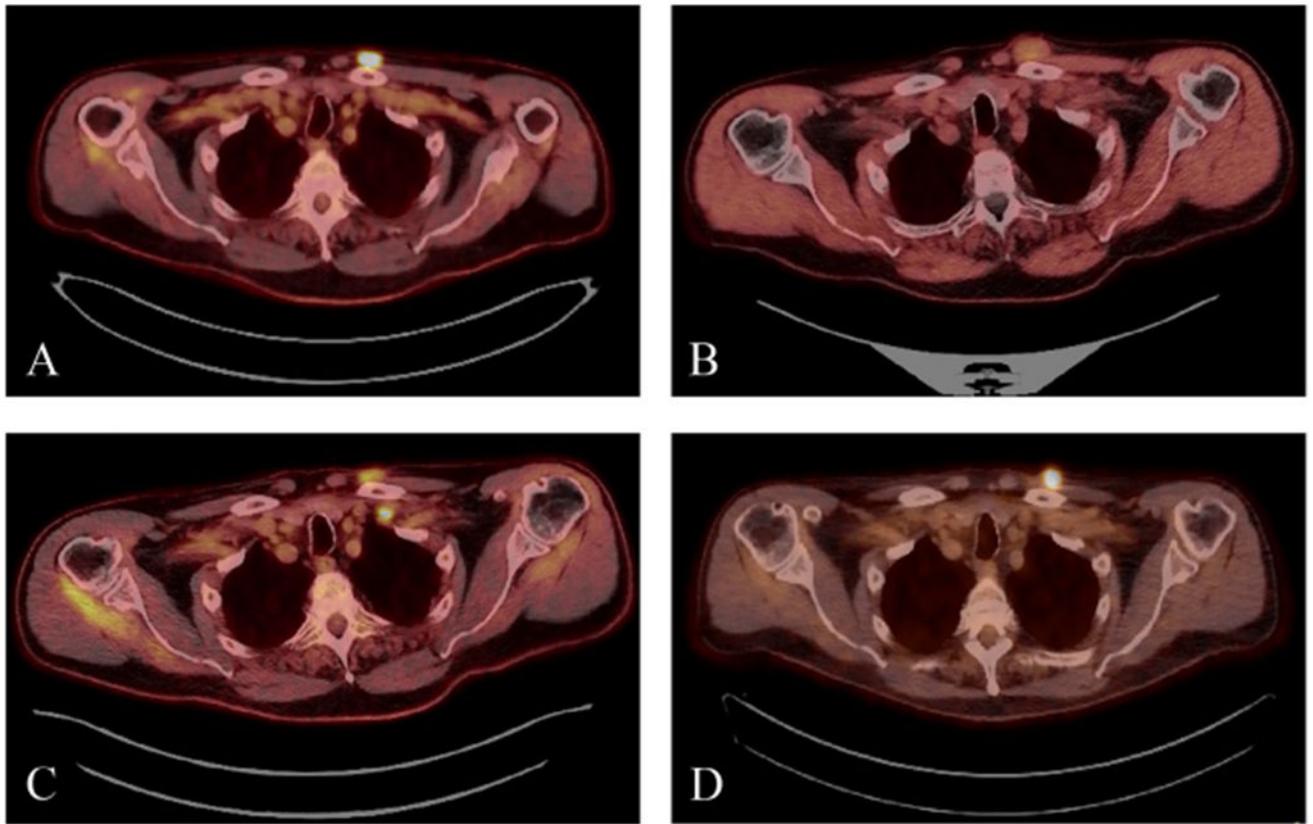
1A: Pre-CAR-T ^{18}F-FDG scan (Day -60). 1B: Pre-CAR-T ^{18}F-FAZA scan (Day -20). 1C: Post-CAR-T ^{18}F-FDG scan (Day +30). 1D: Post-CAR-T ^{18}F-FDG scan (Day +90).

Fig. 1.
Representative PET scan images. Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; ^{18}F-FAZA, [^{18}F] fluoroazomycin arabinoside; ^{18}F-FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography

Table 1

Patient, disease, and scan characteristics

ID	Diagnosis	LDH (U/L)	T/M ratio	[18F]FAZA timing	Bridging therapy and timing relative to [18F]FAZA	CAR-T product	D + 30 PS
05	DLBCL	279	1.35	− 20		Liso-cel	5
04	DLBCL	247	1.19	− 8		Liso-cel	1
03	DLBCL	240	1.09	− 27		Axi-cel	3
11	DLBCL	385	1.09	− 70		Liso-cel	1
17	DLBCL	264	1.08	− 38	GemOx (after scan)	Liso-cel	2
18	DLBCL	163	1.07	− 34		Liso-cel	1
07*	FL	275		− 13		Axi-cel	1
20*	DLBCL	237		− 10		Axi-cel	1
12	DLBCL	235		− 13	Pola-R-CHP (before scan)	Axi-cel	1
22*	HBCL†	222				Liso-cel	
14	DLBCL	204		− 12		CC19703	1
13	DLBCL	199		− 19	R-DHAOx (before scan)	Liso-cel	3
15	DLBCL	192		− 7		Axi-cel	2
23	DLBCL†	186				CC19703	
24	DLBCL	170		− 43		Axi-cel	3
09	MCL	167		− 13		CC19703	1

LDH values (upper limit of normal 243 U/L) represent their most recent value on or before [18F]FAZA scan. Timings of [18F]FAZA scans are shown relative to CAR-T infusion. T/M ratios were only calculated for scans with [18F]FAZA uptake in at least one area attributable to lymphoma. For patients who received bridging therapy, the timings of cycles relative to 1[18F]FAZA scans are shown. All CAR-T products were standard-of-care infusions apart from CC19703, an investigational CD19-directed CAR-T therapy produced at our institution

*
Separate SOC [18F]FDG PET scans before CAR-T therapy showed no evidence of disease at the time of [18F]FAZA scan

†
Did not receive CAR-T therapy as planned due to patient death from CNS relapse (Patient #22) or patient preference (Patient #23)

Abbreviations: *Axi-cel*, axicabtagene ciloleucel; *CAR-T*, chimeric antigen receptor T-cell therapy; *CNS*, central nervous system; *DLBCL*, diffuse large B-cell lymphoma; *D + 30 PS*, 5-point score using Lugano criteria at Day + 30 after CAR-T infusion; *[18F]FAZA*, [18F]fluoroazomycin arabinoside; *[18F]FDG*, [18F]fluorodeoxyglucose; *FL*, follicular lymphoma; *GemOx*, gemcitabine/oxaliplatin; *LDH*, lactate dehydrogenase in U/L (upper limit of normal: 243 U/L); *liso-cel*, lisocabtagene maraleucel; *HBCL*, high-grade B-cell lymphoma; *MCL*, mantle cell lymphoma; *Pola-R-CHP*, polatuzumab/rituximab/cyclophosphamide/doxorubicin/prednisone; *R-DHAOx*, rituximab/dexamethasone/cytarabine/oxaliplatin; *T/M*, tumor to mediastinum ratio; *U/L*, units per liter