Early FDG PET response predicts CAR-T failure in large B-cell lymphoma

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Abstract:
Among patients with large B-cell lymphoma (LBCL) responding to CD19 CAR-T, about half will relapse. It is unclear how to distinguish transient vs. durable response to CAR-T and how to define suboptimal response requiring additional treatment. We assessed early FDG PET response using the 5-point Deauville score (DS) as predictor of outcome after CD19 CAR-T in lymphoma. 171 consecutive patients with relapsed/refractory LBCL treated with axicabtagene ciloleucel or tisagenlecleucel across 3 UK centres were analysed. 130/171 (76%) of patients showed response to CAR-T at the 1-month response assessment: 71 (42%) complete response (DS1-2: n=40, DS3: n=31), and 59 (34%) partial response (DS4: n=36, DS5: n=13, DS4 activity attributed to radiotherapy (DS4RT): n=10). DS response categories at 1 month were significantly associated with the time to relapse (p<0.0001), with HR of 3.0 (95% CI 1.4-6.6) for DS3-4 and HR 19.8 (95% CI 7.8-49.7) for DS5 as compared to the DS1-2/DS4RT group. DS categories were the only significant factor for time to relapse in multivariate analyses adjusting for ECOG PS, LDH, stage, CRP, extranodal involvement and bulk. Long-term survival of responding patients was significantly different according to the Deauville response at 1 month, with 12-month progression-free and overall survival ranging from 77%/87% for DS1-2/DS4RT to 0%/38% for DS5 responders, respectively. Our results indicate that early FDG PET response using Deauville criteria may be used to predict the risk of CAR-T failure and to guide post-CAR-T management in LBCL.

Conflict of interest: COI declared - see note

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Despite high initial response rates, most patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL) treated with CD19 CAR-T will progress. Best overall response rates (ORR) with axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are 50-80%, only half of which are durable.¹⁻³

Pre-treatment factors like LDH and ECOG performance status (PS) are associated with outcome after CAR-T²⁻⁴⁻⁵ and inform upfront patient selection, but have no proven role in post-infusion risk-stratification. Prospective, early identification of patients who will experience transient vs. durable CAR-T responses could in future provide the rationale for targeted combination approaches to counteract CAR-T failure.

Indeed, detection of CAR-T failure prior to frank relapse may improve patient outcomes. Currently, only half of patients with post-CAR-T progression receive further treatment, reflecting the rapid clinical deterioration in this population.⁶ Further, only 20-25% of patients achieve prolonged remission following post-CAR-T therapies. Potentially more patients could be salvaged if CAR-T failure was detected early.

FDG-PET imaging using the 5-point Deauville score (DS) is the gold standard assessment for end-of-treatment response in LBCL.⁷ Interim PET response provides prognostic information in R-CHOP-treated patients⁸⁻¹⁰ and PET-driven treatment strategies are being investigated.¹¹⁻¹³ To date, this has not been evaluated in the context of CAR-T.

In this multicentre retrospective analysis, we assessed early Deauville response after CAR-T in LBCL patients as a potential tool to guide treatment decisions.

We analysed 171 consecutive patients with r/r LBCL treated with licenced CAR-T across 3 UK centres (Freeman Hospital Newcastle, King’s College Hospital London, University College London Hospital) between February 2019-December 2020 who were evaluable for response at 1 month and had at least 3 months follow-up.
CAR-T eligibility was centrally reviewed by the National CAR-T Clinical Panel. CAR-T product choice was at the center’s discretion. Response was assessed locally according to the 5-point DS system.\(^7\) We subclassified DS4 to account for post-inflammatory changes after bridging radiotherapy (RT). Patients with DS4 uptake confined to the RT field were classified DS4\(_{RT}\). FDG-PET scans were performed at 1 month (median 28 days (d), IQR 27-29), 3 months (median 91d, IQR 86-97) and 6 months (median 181d, IQR 175-187) post-infusion. Data were collected retrospectively from hospital records. PET scans were analysed using non-PSF reconstructions.

Transient response was defined as progressive disease (PD) by month 6 after complete response (CR) or partial response (PR) at the 1-month assessment. Ongoing responses at 6 months were classified as durable. Pre-treatment factors were compared using Wilcoxon Mann-Whitney/Kruskal Wallis (continuous variables) or Chi-squared/Fisher’s exact tests (discrete variables). Time-to-PD, progression-free survival (PFS) and overall survival (OS) were analysed using Kaplan-Meier analysis and Cox regression. Time was measured from the 1-month scan until first event. Time-to-PD was analysed using the method of Fine and Grey with non-relapse mortality as competing event.

171 patients were included (130 axi-cel, 41 tisa-cel), with a median follow-up post-infusion of 14.5 months. The median time from approval to infusion was 57d (IQR 49-72). 130/171 (76%) patients responded to CAR-T at the 1-month assessment (Figure1). 40/130 (31%) had DS1-2 response, 31 (24%) DS3, 46 (35%) DS4, and 13 (10%) PR DS5. 46/129 (36%) of responders showed PD at 6 months (transient responders). The study was an NHS service evaluation not requiring separate institutional approval. It was conducted in accordance with the Declaration of Helsinki.

Baseline characteristics are provided in Table1. Patients with transient vs. durable response had higher LDH and CRP pre-infusion. Other baseline characteristics (incl. CAR-T product) did not significantly differ between groups. Deauville categories were significantly associated with durability of response, with a 15% risk of early
progression for DS1-2, 32% for DS3, 37% for DS4 and 100% for DS5 (Table 1; Figure 1).

Of 46 patients with DS4 response, 15 had received RT bridging therapy within 6-8 weeks of the 1-month scan, at which time inflammatory post-RT changes are common. Patients with focal DS4 uptake in the RT field were classified as DS4RT. The DS4RT group behaved similarly to DS1-2 cases with risk of progression at 6 months of 10% vs. 46% for the remaining DS4 cases (Table 1; Figure 1). The 1-month Deauville response was not associated with baseline characteristics apart from higher LDH (p=0.024) and CRP pre-infusion (p=0.0018).

Rather than having one DS cut-off, we considered the predictive power of the 1-month score in two ways. Would we want to forgo further treatment in the low-risk group (low false discovery rate when predicting durable responses), and should the high-risk group be considered treatment failures (high specificity). The DS1-2/DS4RT group showed an excellent false discovery rate (14.0%), and the DS5 group 100% specificity for predicting transient response (vs. 22.5% and 66.3% for a CR/PR cut-point (DS1-3 vs. 4-5)). DS3 and DS4 cases constitute an intermediate-risk group. Time-to-relapse across groups is shown in Figure 1, with HR of 3.0 (95%CI 1.4-6.6) for DS3-4 and 19.8 (95%CI 7.8-49.7) for DS5 vs. DS1-2/DS4RT. DS groups were the only significant factor for time-to-relapse in multivariable analysis.

Long-term survival of responding patients significantly differed according to the 1-month DS (Figure 1). 12-month PFS was 77.1% (DS1-2/DS4RT), 63.5% (DS3), 43.5% (DS4) and 0% (DS5), and 12-month OS was 87.1%, 86.2%, 61.7% and 38.1%, respectively. Patients with SD/PD at 1 month had a 12-month OS rate of 11.5%. The 12-month PFS/OS for the entire cohort was 43.3%/59.7%.

Our results indicate that early FDG-PET response using Deauville criteria may predict the risk of CAR-T failure and be used to guide post-CAR-T management. While patients achieving early DS1-2 remission showed excellent long-term outcomes, patients with DS3-4 response had a 31% risk of early relapse, and 46% for DS4 patients when excluding cases with RT-related activity. DS5 response was associated with dismal outcomes and should be regarded as treatment failure.
Response-adapted trial designs of CAR-T in combination with immunomodulatory agents would be an attractive concept, stratified by the 1-month DS. DS1-2 patients should be spared additional treatment with potential toxicity, but DS3-4 patients with a 30-45% risk of early CAR-T failure might benefit from combinatorial approaches. Biomarkers of early response, such as circulating tumour DNA, might help to further delineate insufficient DS4 responses from post-CAR-T inflammation.\(^{14}\)

In contrast to DS4, all patients with DS5 at 1 month progressed by month 3. Classifying these patients as “responders” raises unrealistic expectations and treatment decisions should not be deferred until formal confirmation of PD, particularly if the disease is amenable to radiotherapy.

Baseline high-risk factors, including LDH and ECOG PS\(^{2,4,5,15}\) inform patient selection pre-CAR-T, but by the time patients have undergone treatment and have responded, an individual patient’s risk will have changed. On-treatment biomarkers including imaging markers of response (e.g. DS or disease metabolic volume kinetics\(^{16}\)) should be incorporated into a dynamic, post-infusion risk model.

Locke et al. demonstrated durable responses in axi-cel-treated patients with higher peak CAR-T expansion relative to pre-treatment tumour burden, and lower IL6, CRP and ferritin on the day of infusion.\(^{4,17}\) In our analysis, the strong association of DS response and outcome was independent of pre-infusion CRP.\(^{,}\) but inflammatory markers were not assessed at the 1-month timepoint.

The difference in PFS by DS category was highly significant and well-separated into 4 prognostic groups. The effect on OS was smaller, likely impacted by post-CAR-T treatments.

In conclusion, our results indicate that early FDG-PET DS categories provide a standardised, broadly available tool to predict durable remission after CD19 CAR-T and could inform early post-CAR-T management and response-adapted stratification in clinical trials.
Data sharing statement
Data can be shared through email request to the corresponding author: andrea.kuhnl@nhs.net.

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Authorship Contributions
A.K., C.R., A.A.K.: designed the research, collected the data, analysed the data, and wrote the manuscript; M.C., M.A.V.M., R.S., M.O., W.T., R.B., V.P., P.E.M.P., D.Y.: contributed to collecting the data and writing the manuscript; T.M., W.O., S.V., G.P., N.M., I.K.: designed the research, collected the data, and wrote the manuscript.

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Table 1: Baseline and on-treatment characteristics of responding patients

| Characteristics                                      | All N=130 | Transient response (N=46) | Durable response (N=83) | P    |
|------------------------------------------------------|-----------|---------------------------|-------------------------|------|
| **Age**, median (range)                              | 59.0 (18 - 78) | 60.5 (18 - 78) | 57.0 (19 - 77) | 0.71 |
| **Sex**, male, no (%)                                | 80 (61.5) | 33 (71.7) | 46 (55.4) | 0.068 |
| **Stage**, III/IV (vs I/II), no. (%)                 | 96 (73.8) | 33 (71.7) | 62 (74.7) | 0.71 |
| **ECOG PS pre-infusion**, no. (%)                    | 2 vs 0-1  | 9 (6.9) | 4 (8.7) | 5 (6.0) | 0.72* |
| **Extranodal involvement**, no. (%)                  | 2 or more sites | 28 (21.5) | 10 (21.7) | 18 (21.7) | 0.99 |
| **Bulk**, (≥7.5 cm)                                  | 30 (23.1) | 14 (30.4) | 16 (19.3) | 0.15 |
| **COO**, no. (%), n=97                               | 40 (41.2) | 10 (31.3) | 29 (45.3) | 0.19 |
| Non-GCB (vs GCB),                                    |           |               |                       |      |
| **Double/Triple hit**, no. (%), n=108                 |           |               |                       |      |
| Double/triple hit (vs none)                          | 13 (12.0) | 6 (15.8) | 7 (10.1) | 0.67 |
| Double/triple expressor (vs none)                    | 16 (14.8) | 5 (13.2) | 11 (15.9) |      |
| **Refractory to last treatment**, no. (%)            | 86 (66.2) | 32 (69.6) | 53 (63.9) | 0.51 |
| **Bridging therapy**, no. (%)                        |           |               |                       |      |
| Systemic                                             | 67 (51.5) | 25 (54.3) | 42 (50.6) | 0.83* |
| RT                                                    | 30 (23.1) | 9 (19.6) | 20 (24.1) |      |
| Combined modality                                    | 5 (3.8) | 1 (2.2) | 4 (4.8) |      |
| **LDH pre-infusion**, no. (%), n=104                  |           |               |                       | 0.041** |
| >ULN (vs normal)                                     | 50 (48.1) | 20 (55.6) | 29 (43.3) |      |
| >2ULN (vs normal)                                    | 12 (11.5) | 6 (16.7) | 6 (9.0) |      |
| **CRP pre-infusion**, median (range), n=104          | 11.2 (0.5 - 235) | 22.5 (1 - 235) | 6.8 (0.5 - 160) | 0.003 |
| **CAR-T product**, no. (%)                           |           |               |                       |      |
|                | Axi-cel  | Tisa-cel | Grade ≥3 CAR-T toxicity, no. (%) | Deauville score at 1 month, no. (%) |
|----------------|---------|---------|---------------------------------|-------------------------------------|
|                | 107 (82.3) | 39 (84.8) | 67 (80.7) | **0.56** |
|                | 23 (17.7) | 7 (15.2) | 16 (19.3) |            |
| CRS            | 11 (8.5)  | 6 (13.0) | 5 (6.0) | **0.20** |
| ICANS          | 22 (16.9) | 8 (17.4) | 13 (15.7) | **0.80** |
| DS 1-2         | 40 (30.8) | 6 (13.0) | 34 (41.0) | **<0.0001** |
| DS 3           | 31 (23.8) | 10 (21.7) | 21 (25.3) |            |
| DS 4           | 46 (35.4) | 17 (37.0) | 28 (33.7) |            |
| DS 5           | 13 (10.0) | 13 (28.3) | 0 |            |

Exclusion of n=1 patient with non-relapse death prior to 3-month assessment (not evaluable for durability of response). P-values are Wilcoxon Mann Whitney (continuous) or Chi-squared (discrete, except: *Fisher's exact test and **chi-squared for trend).

COO: cell-of-origin
ULN: upper limit of normal
CRS: cytokine release syndrome
ICANS: Immune effector cell-associated neurotoxicity syndrome

**Figure 1:** Outcome according to the 1-month DS. (A) Dynamics of response, (B) Time-to-relapse, (C) Progression-free survival, (D) Overall survival.
