High frequency of hyperglycaemia observed during CAR T-cell treatment

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LETTER

High frequency of hyperglycaemia observed during CAR T-cell treatment

CD19-directed chimeric antigen receptor (CAR) T-cell therapy is an emerging treatment for people with refractory/relapsed large B-cell lymphoma (LBCL) and other B-cell-related malignancies. Autologous T-cells are genetically modified by transducing them with a CAR-construct, consisting of a CD19-recognition domain, a costimulatory domain (CD28 or 41BB) and a CD3ζ intracellular signalling domain.[1] This treatment may offer the person high response rates, increased survival and long-term remission.[2]

However, adverse events of this therapy are frequent and include (up to 90% of cases) cytokine release syndrome (CRS) and (up to 60%) immune effector cell-associated neurotoxicity syndrome (ICANS).[3,4] The occurrence of CRS and ICANS is triggered by the interaction of the CARs with their specific antigen (hence CD19 for LBCL), which results in the activation and proliferation of T-cells and the subsequent secretion of cytokines and chemokines. As a result of this interaction, levels of inflammatory cytokines increase to supra-physiologic levels.[5] As increased levels of cytokines, especially interleukin-6 (IL-6), are known to correlate with the occurrence of insulin resistance,[6] we hypothesized that hyperglycaemia is a frequent finding during CAR T-cell treatment. Given the impact of hyperglycaemia on cytotoxic T-cell function[7] and the well-established association of glucose dysregulation with outcomes, including mortality and morbidity,[8] such as the increased risk of infections, prolonged hospital stay and, therefore, higher costs there is a rationale for early recognition of glucose dysregulation. To establish the frequency of hyperglycaemia and its impact on the duration of hospitalization amongst participants receiving CAR T-cell therapy we performed a retrospective study.

All adult participants receiving CAR T-cell therapy for LBCL in the University Medical Centre Groningen (Groningen, The Netherlands), between October 2017 and March 2022, with data on point of care (POC) or vena punction glucose concentrations during admission were included. According to current guidelines, the presence of hypo- and hyperglycaemia was defined as glucose <3.9 mmoL/L and glucose >7.8 mmoL/L.[9]

During the study period, 61 participants received CAR T-cell therapy. For two participants, data on glucose levels during admission were lacking. Consequently, 59 participants were included in the analysis. From 11 participants POC measurements were available. The glucose levels from the other 48 participants were determined from vena punctions. Of the participants, 68% were male, mean age was 59 (±11.6) years, and mean body mass index (BMI) was 25 (±5) kg/m^2. 5% of the participants had stage 1 disease, 12% stage 2, 19% stage 3, and 64% stage 4. Three participants were diagnosed with diabetes mellitus prior to hospitalization: one participant with Type 1 diabetes and two participants with Type 2 diabetes.

Dysglycaemia was present in 25 participants (42%). All these participants experienced hyperglycaemia (glucose >7.8 mmoL/L). There was one hypoglycaemic event in an insulin-treated person with a history of type 1 diabetes. When excluding the participants with known diabetes ($n = 3$), the percentage of participants experiencing hyperglycaemia was 39%. During hyperglycaemic episodes, the average glucose concentration was 13.2 (±4.4) mmol/l with a maximum concentration of 27.1 mmoL/L.

The length of hospital stay of participants that experienced hyperglycaemia was significantly longer than those without hyperglycaemia: 16 (±7) vs. 10 (±3) days, ($p < 0.0001$) (Figure 1). Additionally, we examined the occurrence of CRS and ICANS amongst participants with and without hyperglycaemia. Results show that all 25 participants (100%) with hyperglycaemia also had CRS and 16 (64%) had ICANS. In comparison to participants who did not experience hyperglycaemia, these numbers are 21 (65%) and 5 (18%), indicating a relation between the occurrence of hyperglycaemia and the occurrence of CRS and ICANS ($p < 0.0003$ and $p < 0.0002$).

Twenty participants (34%) received dexamethasone to treat ICANS. Dexamethasone is a steroid with several side effects, of which hyperglycaemia is the most common. Of these 20 participants, 15 had hyperglycaemia (75%). Interestingly, 8 of these participants (53%) already had hyperglycaemia before receiving dexamethasone. Of the 39 participants that did not receive dexamethasone, 10

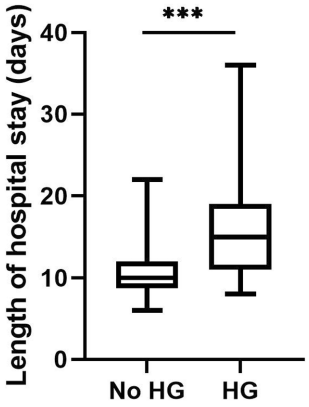

FIGURE 1 Distribution of length of hospital stay comparing participants with and without hyperglycaemia. Data represent the median, interquartile range, minimum and maximum. HG, hyperglycaemia

(26%) experienced hyperglycaemia. Altogether, excluding the participants with diabetes and the participants with hyperglycaemia after receiving dexamethasone, 15 participants (31%) had hyperglycaemia with an unknown cause.

Despite the limitations of a single-centre, retrospective study these data emphasize the high frequency of hyperglycaemia during CAR T-cell therapy. Given the deleterious effects of hyperglycaemia in general, and possibly also in this particular patient population, these observations may be of importance to guide supportive care during CAR T-cell therapy. To this extent, we hypothesize that the use of real-time glucose monitoring using glucose sensors allows more precise identification of dysglycaemia (as compared to POC measurements) and that this may lead to better outcomes. In addition, given the possible association of cytokine release, insulin resistance and hyperglycaemia this may also lead to early detection of CRS/ICANS.

KEYWORDS

CAR T-cell treatment, hyperglycaemia, large B-cell lymphoma

CONFLICT OF INTEREST

TvM has an advisory role by the for-profit health care company Kite/Gilead, Janssen and has received research funding from Genentech, Celgene/BMS. The remaining authors have no relevant conflict of interest to declare.

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