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Monitoring of toxicities induced by Chimeric Antigen Receptor T-cell therapy: Protocol for a phenomenological study on the experiences of nurses.

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Study protocol

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ABSTRACT

Introduction: Chimeric Antigen Receptor T-cell therapy (CAR-T) represents the most recent immunotherapy's innovation to cure some refractory and/or relapsing haematological tumours. However, because of the life-threatening toxicities it might cause such as *Cytokine Release Syndrome* and *Immune Cell Associated Neurotoxicity Syndrome*, patients are closely monitored by nurses for the early identification of toxicities during the post-infusion phase of CAR-T cell therapy. Exploring the nurses' experience with respect to any difficulties related to the monitoring is important since these issues can be perceived by patients and affect the nurse-patient's caring relationship, considered as a shared lived experience between the patient and the nurse.

Aim: This study aims to investigate haematology nurses' lived experience with monitoring CAR-T's induced toxicities.

Materials and methods: A qualitative study following Cohen's phenomenological methodology will be conducted through semi-structured interviews in a sample of Italian nurses working in haematology units, who have had previous experience in the management of patients undergoing CAR-T therapy for at least two months and who have performed the monitoring for the same months of experience; the interviews will be audio-recorded and then transcribed verbatim. Two researchers will carry out the manual analysis and interpretation of the collected data independently, identifying themes and sub-themes.

Conclusion: To explore the nurses' experiences in this field could facilitate the identification of the educational needs, at individual and group level. Despite it is important to consider contextual variables, the findings of this study could contribute to develop evidence supporting advanced and specialized nursing care in the haematological setting.

Keywords: hematology, nursing, CAR-T therapy, phenomenological, qualitative.

INTRODUCTION

Chimeric Antigen Receptor T-cell (CAR-T) therapy is the latest immunotherapy approach for the treatment of certain resistant or relapsing haematological cancers [1], including: Acute Lymphoblastic Leukaemia, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and mantle cell lymphoma. However, despite being designed to act selectively in eliciting a targeted immune response against neoplastic cells, anti-CD19 CAR-T cell therapy is not free of risks and even serious side effects. The most frequent toxicities are Cytokine Release Syndrome (CRS), reported in 57% to 93% of patients who underwent CAR-T [2], and Immune Effector Cells Associated Neurotoxicity Syndrome (ICANS), which occurs in 20% to 70 % of patients [3]. Nevertheless, while they are often manageable and reversible, they can prove fatal, requiring close patient monitoring, early recognition of toxicities, and prompt intervention to reduce morbidity and mortality [3].

To achieve this, patients are closely monitored by nurses after infusions following specific protocols and procedures adopted in the operating units. More specifically, monitoring by nurses includes the assessment of vital parameters as well as typical signs and symptoms of Cytokine Release Syndrome (CRS) and neurological toxicity (ICANS) [4]. Specifically, to facilitate the identification of early manifestations of neurotoxicity, close monitoring using validated nursing instruments [5] is necessary, including the handwriting test and the quantification of the *"ICE - Immune Effector Cell-associated Encephalopathy score"*. The latter enables the mental status of patients to be assessed by identifying four ICANS grades (numbered 1 to 4) according to the presence or absence of consciousness impairment, seizures, motor alterations and symptoms of high intracranial pressure [6].

Thus, monitoring enables the nurse to conduct a targeted assessment of the patient's condition in the post-infusion phase, which is decisive for a timely approach to CAR-T toxicities by activating the entire multidisciplinary team. Said approach effectively relies on the meticulous execution of the

objective examination, where a high patient assessment frequency [7] enables the practitioner to perceive even the most subtle changes in the patient's psycho-physical condition.

A recent study showed that for patients undergoing CAR-T cell therapy and experiencing significant side effects, continuous monitoring by nurses provides them with a sense of security, and they particularly appreciate the time nurses devote (in addition to monitoring activity) to engaging in dialogue and expressing an interest in their state of health [8]. Therefore, it is essential to acquire deeper insights into the challenges nurses face during the complication monitoring phase, considering that patients may sense such difficulties, which may, consequently, affect the caring relationship established during this crucial assistance.

As a fundamental aspect of nursing practice, the nurse-patient relationship is part of a broader context in which nurses use their senses, knowledge, and experience to exercise professional judgment and discernment when providing care in specific situations [9]. As such, a thorough examination of patients' care experience and the related outcomes must also be conducted with due consideration for the experiences narrated by the haematology nursing staff, since the practice of nursing care necessarily implies a shared experience of the relevant dynamics [10,11].

However, the topic of nursing care in the management of patients undergoing CAR-T cell therapy is a relatively new area of investigation, so few studies have been conducted in the field of nursing. The limited literature has only investigated the experience of patients undergoing CAR-T therapy and/or their caregivers without delving into the experience itself and the meaning attributed to this experience by those who care for patients and/or interact with and support caregivers [12-14]. Moreover, only one study, conducted in China, investigated the experience of a group of oncology nurses in managing this specific subpopulation of patients but was focused on nursing competence [15]. This study did not examine the nurse's key role during the toxicity monitoring phase in-depth, and the main focus was on aspects related to nursing skills rather than the significance of the experience.

To date, to the best of our knowledge, no study has explored nurses' experiences in the monitoring and care of this specific category of haematological patients, even though the aforementioned scientific literature frequently emphasises the importance of nursing care at all stages of the clinical care process and particularly during the post-infusion phase.

Study aim

The purpose of this study is to explore the experience of nurses caring for haematology patients during the monitoring of the main toxicities associated with CAR-T therapy.

MATERIALS AND METHODS

Study design

A hermeneutical phenomenological study will be conducted according to Cohen's method [16]. A summary of the planned operating times for the study is shown in Table 1.

Study phases	Activities	Estimated duration (time)	Follow-up
Definition and planning	Review and analysis of the literature, research question	1 month (September)	Focus: researchers; stakeholders.
	Development of the research design, context analysis, selection of potential data acquisition centres	2 months (October–November)	
	Drawing up of draft protocol	2 months (December–January)	
	Review and finalisation of the protocol.	2 months (February–March)	
	Authorisations by the participating centres. Request for an opinion form the Ethics Committee (EC)	2 months and 15 days (April–June)	
	"Bracketing" process and exchanges between researchers	15 days (June)	
2. Recruitment of participants	Recruitment of data acquisition centre and participants	15 days (July)	Focus: participants

	Finalisation of the sampling plan		
	Informed consent		
Data collection	Pre-test data collection tool (pilot interviews) and finalisation of interview questions	15 days (July)	
	Conduct of interviews and return of transcripts	1 month (August–September)	
Data analysis	Data preparation: transcription, reading of interviews (units of meaning)#	1 month (September–October)	Focus: texts (transcribed interviews)
	Data codification and reduction process		
	Thematic analysis		
	Writing and editing		
	Discussion and sharing of emerging themes (provisional)	15 days (October)	Focus: researchers, participants
Final report	Drafting of the final report, manuscript.	1 month (November)	Focus: scientific community, stakeholders

Table 1. Envisaged timeline for the study (2023–2024).

The phenomenological approach is based on the understanding of questions of meaning and the actual experiences of informants [16] by combining the methodological properties of descriptive (Husserlian) and interpretative (Gadmerian) phenomenology. The former descriptive scope aims to describe the experiences of individual members of the cohort under study after a preliminary phase in which the researchers set aside prejudices and preconceptions about the phenomenon under investigation ("*bracketing*"). This is crucial to reduce the influence of such prejudices and preconceptions on the subsequent phase, in which the themes and data emerging from the interviews are respectively extrapolated and analysed. The interpretative intent, on the other hand, examines and interprets the reported experiences in depth [17]. Therefore, since this methodological approach focuses on understanding questions of meaning and the real-life experiences of the respondents [16], it is particularly suited to nursing-related research and topics seldom explored in the literature. It is also instrumental in the broader context of a working organisation for identifying perceived needs and the solutions that can best address them [16].

Participants and study context

The participating cohort will be recruited from haematology operating units in Italy, identified at the national level among the accredited haematology and onco-haematology centres of advanced specialisation for the treatment of leukaemias and lymphomas, compliant with specific requirements and authorisations for cell therapies as prescribed by AIFA, the Italian Medicines Agency.

Intentional ("propositional") sampling will be carried out within each data collection centre according to a homogeneity criterion [18,19] to investigate differences and variations within a relatively homogeneous sample [18, 20] in relation to experience in handling the monitoring cards of patients subject to complications associated with CAR-T therapy. This sampling will enable the researchers to deliberately select a cohort of nurses who possess specific expertise and experience in the management of complication monitoring based on a set of pre-established criteria (inclusion and exclusion criteria); this is of fundamental importance in order to obtain a sample capable of providing meaningful, subject-specific information as well as credible and reliable explanations of the phenomenon under study, irrespective of the cohort size [21].

Sampling will continue until data saturation is reached, understood as a process of conducting interviews sequentially until the concepts expressed by the respondents are repeated several times without introducing new concepts or themes [22]. The unitary element of analysis will coincide with the experience under study; therefore, considering that a single respondent can generate many concepts, large samples in numerical terms are not necessarily useful for generating a comprehensive dataset with respect to the purpose of the study and the phenomenon of interest [23]. Indeed, in a qualitative dataset, most new information is generated early in the process and generally follows an asymptotic curve whereby new information declines after a small number of interviews or data analyses [24]. In particular, with regard to studies marked by a high level of population homogeneity, the literature indicates that a sample of six interviews is sufficient to foster the development of meaningful themes and useful interpretations related to the phenomenon under

study [25]. Therefore, in accordance with the above and considering that the scope of phenomenology is to explore the common features of real-life experiences gleaned from data provided by only a few individuals who have experienced a particular phenomenon as subjects capable of providing detailed and in-depth information [23], in accordance with claims stated in the literature regarding sample sizes for phenomenological studies, which generally vary from 5 to 25 respondents [26], a sample cohort of 6 to 12 nurses is deemed acceptable for this study.

Inclusion and exclusion criteria

Subject to voluntarily agreeing to participate in the study by signing the informed consent, the study will include all nurses who provide direct patient care at the data collection centres and who have passed the probationary period within the organisation for the inclusion of newly recruited or newly assigned nurses in the operating unit. The selected nurses will have had appreciable experience (for a minimum of two months) in managing patients undergoing CAR-T therapy and must be practised in the use of assessment tools (at least on one occasion) during the same months of experience.

Nurses who provide day hospital care at the operating unit and those in exclusively organisational roles will be excluded from the study.

Data collection tools and study procedures

Interview

For data collection, we developed a draft semi-structured interview outline with open-ended questions that will allow participants to express themselves freely [16]. The interview outline was drawn up considering previous similar studies carried out in the haematology field [12-15] and following discussion within the research group and discussion with expert haematology clinicians working in an accredited Italian haematology and oncohaematology centre with high specialisation in the treatment of leukaemias and lymphomas, meeting specific requirements and authorisations

for cell therapies.

The envisaged main questions are as follows: *"Please could you tell us about your experience with monitoring CAR-T therapy-induced toxicities for patients in the Haematology Unit?;* "*How would you describe your experience using CRS and neurological toxicity monitoring tools such as the ICE score and the handwriting test?"; "Regarding your experience, what were the positive and negative aspects? Can you please provide some examples?".* If further investigation of the emerging themes is required, the researcher will add specific questions to the interview to clarify the contents expressed. Finally, the interview will conclude by asking participants if they need to add anything else or report anything specific to what has already been said. This will be solicited by the following question: *"Do you have any further comments or suggestions?"*; in the event of a negative response, the interview will be considered completed.

In addition, demographic data will be collected from participants relating to age, gender, level of education, marital status, years of work as a nurse, years of work as a nurse in the current haematology unit, previous clinical experience (work areas/clinical specialities in which you have served as a nurse).

Once the necessary ethical authorisations for study commencement have been obtained, a limited number of pilot interviews (at least two) will be conducted to test the draft interview outline and possibly fine-tune it before proceeding with the study.

Data collection

In keeping with the method proposed by Cohen and co-authors [16], before conducting the interviews, all researchers will undertake a process aimed at suspending, i.e. *bracketing* their personal expectation bias, assumptions, and preconceptions, if any, regarding the phenomenon being studied. According to the proposed method, this approach is crucial as it reduces the likelihood of the researcher's judgements influencing the extrapolation of themes from the

interviews [16].

Each interview will be *conducted face-to-face*, individually, by a researcher with professional experience in the field of haematology, but who is not part of the team working in the data collection centre. In addition, interviews will be conducted by prior agreement with the individual participant in a location that ensures participants feel comfortable, facilitating spontaneous and natural responses [16].

Subject to written informed consent, each interview will be recorded using protected digital tools that are not accessible except to researchers so that they can subsequently be transcribed *verbatim* for data analysis purposes. Subsequently, the transcripts will be returned to the interviewees for comments or clarification. Considering the impossibility of establishing a predetermined interview duration, given the purpose of the study and the complexity of the phenomenon to be examined, a time of between 40 and 70 minutes is envisaged for each interview.

Data analysis

Two researchers will independently analyse the data extracted from the interviews using a manual approach [27,28]. In accordance with the method of Cohen and co-authors [16], the data analysis will comprise the following principal phases: (I) The Data Preparation Phase, in which the interviews, previously recorded, will be transcribed *verbatim and* transferred to digital media; in this phase, the units of analysis (words, phrases or themes) will be selected, and a repeated and in-depth reading of the transcripts will be carried out, through the process of immersion in the data [29] to become familiar with the transcripts and highlight the essential features within each interview [30,31] while simultaneously carrying out an initial interpretation of the contents that will guide the codification of the data in the subsequent analysis phases [16]. (II) the Data Codification and Reduction Process: in this phase, the researchers will reorganise the contents of the interviews, grouping content pertaining to the same subject, eliminating any digressions that stray from the

phenomenon under study and simplifying the respondents' spoken language without actually modifying the content expressed; a “line by line” analysis of what the participants reported will be carried out to provide “a label of meaning” to each part of the text [16], starting the reduction process while maintaining the overall essence of the contents expressed [16]. (III) Thematic Analysis: the purpose of the thematic analysis is to systematically describe and interpret the meaning of the qualitative data generated by the interviews, generating themes that will be finally analysed and presented [32]. At this stage, once an overall interpretation of the contents has been obtained, sentences in the text will be underlined by writing “headings” in the margin of the text that will represent the provisional names and/or themes assigned to the most salient content aspects [16,33-36]. To this end, colours may be used, or specific text segments may be highlighted to indicate potential interpretative patterns instrumental to identifying data segments; similarly labelled interview passages will then be grouped and appropriately reorganised [16]. In this way, as the main headings are identified, the extracted data will be collected and grouped manually within each codification, generating an initially unrestricted list of categories [36]. (IV) The Writing and Editing Process [35]: a reflexive writing and rewriting process will initially identify themes that will be followed by an in-depth examination and comparative analysis of the same within a broader framework to validate the overall meaning derived from the contents of the interviews [16]. The lists of categories will then be grouped into higher-order headings of broader scope capable of describing and augmenting the understanding of the phenomenon, thereby generating new knowledge [36]. The category reduction process will involve pooling similar or related observations and comparing data from within the same category with data from other categories [36]. Finally, the abstraction process will make it possible to formulate a general description of the phenomenon under study by formulating specific categories (general and subcategories) that will be named using words that reference their content [29]. A deep probing of the meaning of the interview content will lead to an overall understanding of the respondents’ real-life experiences as expressed within the

emergent themes. This understanding will be supported by recourse to margin notes as part of the hermeneutic process underlying the transformation of the text fields into a coherent narrative [16,37]. (V) Following thematic analysis, the researchers will discuss the provisional emergent themes with the other members of the research team, including qualitative research and haematology nursing experts. Subsequently, the provisional themes will be returned to the participants to verify that the researchers had correctly interpreted their submissions, and only then will they be confirmed.

Methodological rigour

To minimise social desirability bias, the interviews will be conducted by a researcher who has no previous involvement with the study centre in a professional capacity. The researchers tasked with analysing the data will also have previous oncological work experience, albeit in different settings other than the data collection centre; this will underpin the credibility of the research process. The practice of *"bracketing"* will promote critical thinking among researchers to ensure methodological rigour and avoid the contamination of individual judgement during data analysis [16]. The practice of "bracketing" will promote critical thinking among researchers, ensuring methodological rigour and avoiding the contamination of individual judgement during data analysis [16]. Furthermore, to reinforce the collaborative relationship between participants and researchers and confirm the accuracy of outcomes, respondents will be asked to provide feedback on the (provisional) themes identified (*member-checking* of participants); they will also be offered the opportunity to add details or clarifications regarding their experience, if necessary [38].

Ethical considerations and protection of data confidentiality

The study was submitted to an independent Ethics Committee, which expressed a favourable opinion on the conduct of the study (Project identification code 1697/CEL – CARTINF Study;

approval number 389|13/06/2024).

Nurses' involvement in the survey will be voluntarily, and the semi-structured interviews will be preceded by asking study participants for written consent to their participation, recording of the interviews, and processing of related data. They will also receive all information about the study's purpose, how data is collected and managed, and its confidentiality.

Anonymity will be guaranteed as prescribed by prevailing legislation on the processing of personal data and respect for privacy (Italian Laws nos. 675 & 676 of 31 December 1996, Official Journal of 08/01/1997, Article 7 of Italian Legislative Decree no. 196 of 30 June 2003 and European Privacy Regulation EU 2016/679, General Data Protection Regulation – GDPR). Relevant data will be strictly used for the purposes of the study.

Presentation of results

The results of the study will be presented in narrative form, reporting excerpts from interviews in support of the identified themes and sub-themes. Furthermore, graphic aids in the form of charts and tables will be included to enhance visualisation of the interview outcomes and related analyses (e.g. with respect to the originally codified themes) in terms of response frequencies and percentages [32]. In particular, tables may be used to express thematic outcomes quantitatively (e.g. organisation of the various themes according to the number of codes they contain), the intent being to facilitate and not replace the presentation of the interview extracts in narrative form.

DISCUSSION

To date, the real-life experiences of nurses responsible for monitoring CAR-T therapy toxicity have not been significantly studied or reported in the literature. No such research has been undertaken in Italy, while, at an international level, only a recent study conducted in China investigated the views of nurses caring for this patient category to assess the skills and knowledge required for the specific

care context [15]. Yet, given the broader scope of contextual acquired knowledge, close investigation into the aspects of the nursing experience with respect to one of the salient aspects of caring for this patient segment is of paramount importance. Such aspects manifestly impact clinical practice and enrich caring skills, not only in terms of scientific knowledge, but also in relation to intrinsic, humanistic, relational and affective aptitudes [39-42]. Indeed, nurses also expand and refine their knowledge over time by elaborating their clinical practice experiences [43]; in this sense, the findings of this study could be beneficial in understanding how experience, not only educational but also clinical, can provide benchmarks for adapting and refining onco-haematology nursing care concerning the delicate and complex phase of complication monitoring in patients undergoing CAR-T cell therapy. As highlighted in the literature, in fact, the cumulative process of structuring and drawing on real-life experience engenders a body of knowledge that represents a resource for interpreting past and present experiences and, at the same time, anticipating and supporting the shaping of future experiences [43]. Ultimately, with regard to the nursing skills specific to these care contexts, the study findings may provide useful information for the development of advanced skills aimed at implementing clinical practice improvement projects. The latter would strive to optimise care time using appropriate and effective documentation, enriching the effort dedicated to a caring relationship with patients that ensures optimal quality of care and clinical safety. Moreover, appreciation of the meanings attributed to individual experiences may enhance the crucial role of haematology nurses in the management and monitoring of treatment-related toxicity, which is acknowledged as an influential factor in the overall patient experience and related care outcomes [44]. Reflecting on the advanced expertise of affirmed professionals working in multidisciplinary teams as well as on individual and group needs may increase professionals' awareness of the importance of sharing their real-life experiences. Accordingly, the methodology devised for this study and its findings may serve to develop organisational strategies aimed at effective professional training in contexts involving the introduction of specific nursing activities instrumental to the

introduction of new clinical procedures and protocols. Indeed, there is a need to invest in nursing leadership and governance in order to promote further empowerment of the role of the function and to respond to the need for strong nursing standards [45] in oncohaematology practice. Lastly, the findings of this study may also stimulate thinking within the universities since, in order to invest in university education that produces advanced nursing expertise within multidisciplinary teams, it is essential that curricula are appropriately aligned with health priorities and emerging issues, both from a global and national perspective [46].

CONCLUSIONS

The introduction of innovative and complex procedures necessitates the development of healthcare and educational strategies that support the advancement and recognition of nursing expertise in specific care settings. Thus, building on the individual insights of each participant, the findings of this study may reveal hitherto unknown aspects of haematology nursing and contribute to the recent debate on advanced nursing skills by providing a detailed understanding of the experiences of nurses in haematology care.

Limitations of the study

The study may entail some limitations; the results may be affected by contextual organisational variables, which are difficult to generalise to all clinical scenarios, although they are easily transferable to a variety of contexts, also considering that the centres approved for the administration of CAR-T cell therapy meet the same national standards defined by AIFA. Nonetheless, to further ensure the credibility and transferability of the results to other organisational contexts, nurses should be selected from several approved centres throughout Italy. In addition, given the subject matter, some interviewees might place undue emphasis on the positive aspects of direct patient care while more readily identifying critical organisational factors, which do not

directly impact their role identity as individuals and professional team members to the same extent.

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Conflicts of interest

None.

Authors' contributions

Concept and methodology: VS, LG, DC, GC; preparation and drawing up of the original manuscript draft: VS, LG, DC; supervision: GC, DC; methodology; writing, revision, and editing: LG, FG, CT, RN, AT, FP. All authors contributed to the finalisation of the study protocol and approved the final manuscript.

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