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Evaluating the Trade-offs of CAR-T cell Therapy through the correlation of Societal perceptions, Split dosages, and B-cell aplasia

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ABSTRACT

This study evaluates the trade-offs of Chimeric Antigen Receptor (CAR) T-cell therapy by correlating B-cell aplasia under split dosage regimens with the societal perceptions of Taiwanese parents. While CAR-T cell therapy offers significant oncological benefits, its severe toxicities pose substantial physical and psychosocial burdens. Existing literature suggests split dosing mitigates these toxicities, yet its impact on B-cell aplasia and parental perceptions of these trade-offs remains underexplored.

Utilizing a quantitative descriptive approach, this study combined a computational simulation (CARTmath) with a cross-sectional survey of 59 Taiwanese parents. The simulation modeled CAR-T cell expansion and B-cell depletion under single versus fractionated dosages. Simultaneously, the survey assessed parental values regarding treatment risks, benefits, and logistical factors.

Simulation results indicate that split dosing yields a more gradual and controlled depletion of B-cells, hypothetically suggesting that the velocity of depletion may serve as a more reliable clinical marker for treatment efficacy than absolute concentration. Concurrently, survey data revealed an underwhelming awareness for CAR-T therapy among parents, who definitively prioritized safety outcomes—specifically high remission rates and reduced toxicity severity—over logistical concerns like cost or convenience. Furthermore, prolonged toxicities, such as multi-year B-cell aplasia, significantly reduced parental acceptability of the treatment.

Thus, in conclusion, the computational data supporting more plateaued toxicity under split dosages strongly aligns with Taiwanese parents' prioritization of priority safety, depicting the necessity of integrating and further developing the perspectives of this research paper.

INTRODUCTION

Research on the effects of split dosages on B-cell aplasia in CAR-T cell therapy, demonstrates both a scientific lens and a societal perspective on cancer therapy. CAR-T cell therapy for oncological applications has been available for a few decades and has gained popularity in recent years. It's utilized by genetically engineering a person's T cells to express chimeric antigen receptors that enable them to recognize and attack cancer cells. *A Nature Reviews Clinical Oncology* article states that, despite recent breakthroughs in the clinical application of the therapy, effective treatment to fully mitigate its toxicities—including neurotoxicity, cytokine release syndrome, and B-cell aplasia (1, 2)—remains limited**.** As a result, B-cell aplasia is often used as an indicator of therapy duration. Concurrently, recent literature suggests a negative correlation between split dosing and toxicity: as treatment duration increases and doses are reduced, toxicity decreases (3, 4). In correlation with B-cell aplasia, it has yet to be researched under split dosages, and so, the unpredictability of the cancer treatment has yet to be adequately reviewed. Integrating patient perspectives, considering the uncertainty of the treatment, recent literature has addressed the psychosocial and physical challenges associated with the mental burden of undergoing CAR-T cell therapy. However, reviews have yet to reflect perceptions of the risks and benefits among patients, parents, and society as a whole. Based on the prerequisite information, this study explores whether participating Taiwanese parents are more likely to perceive split-dose CAR-T cell therapy as an acceptable treatment strategy compared to single-dose treatments because its reduced toxicity—a heavily valued factor—suggests mitigating concerns such as prolonged B-cell aplasia, indicating that reduced risk is prioritized over treatment duration in parental decision-making. Exhibiting this relationship, this study combines survey data and computational simulation to examine variations in split dosages' impact on simulation outcomes and societal opinions regarding risk and benefit.

LITERATURE REVIEW

Coverage of Current Literature

Recent insights into CAR-T cell therapy emphasize the importance of managing toxicities, using B-cell aplasia as a marker, and accounting for societal perspectives. B-cell aplasia has been widely suggested as an effective indicator of CAR-T cell therapy duration, as it reflects unintentional targeting of B cells and therefore indicates the persistence of effective treatment.

B-cell aplasia is commonly used as a surrogate marker; studies often overlook its association with increased susceptibility to disease and infection (1, 2, 3). Incorporating previously conducted experiments, fractionated CAR-T dosing over 2-3 days has exhibited an association with lower levels and mitigation of severe CRS and neurotoxicity compared to single infusions, yet B-cell aplasia is not investigated under the presented context. As presented, the existing literature provides limited research on the occurrence of B-cell aplasia under fractionated dosing and insufficient attention to patient and societal

perspectives. In parallel, qualitative and survey studies address the significance of psychosocial and physical challenges associated with the mental burden of patients undergoing CAR-T cell therapy, whereas a gap still persists covering the perceptions of benefits and trade-offs. Thus, the current literature presents inadequate research on B-cell aplasia under fractionated dosing, patient perspectives, and biomarkers.

Split dosing and Toxicities

Current clinical trials and systematic reviews focus on strategies to mitigate toxicities such as CRS and neurotoxicity, as they are significant factors impacting both patients' mental and physical health, alongside the societal perspectives of benefits and tradeoffs. Across systematic reviews and clinical trials, studies have consistently reported high frequencies of treatment-related adverse events and toxicities, but have also suggested a reduction of toxicity while preserving high remission rates in dose fractionation.

Delving deeper into CAR-T cell therapy, a widely studied factor associated with reduced toxicity is split dosing, which has been shown to be negatively correlated with toxicity density after treatment within numerous biological assessments and clinical trial data. Split dosing is a treatment plan where a single medication is given at different times and different dosages, which has been found to reduce some side effects in treatments such as antidepressants, CAR-T cell therapy, and many more (4, 5).

In addition to the effectiveness observed with split dosing, a significant research gap remains covering the relationship between CAR-T cell therapy and B-cell aplasia, as prior studies have predominantly examined its effects on Cytokine Release Syndrome and Neurotoxicities. Evidently, CAR-T cell therapy fractionation studies primarily focus on CRS and neurotoxicity outcomes, whereas few report the trajectories of B-cell aplasia under split dosages. Previous studies collectively reinforce that administering CAR-T cell therapy over time, rather than a single-dose infusion, can mitigate the severity of treatment-related toxicities (5, 6). Concurrently, despite the significant impact of toxicities, specifically B-cell aplasia, on patient health, alongside an influential factor for tradeoffs, its presence is consistently overlooked in treatment research (7). Simultaneously, supporting studies imply that fractional dosing enables individualized modifications, thereby allowing for a better balance of efficacy and safety compared to single dosages.

Contradicting scientific perspectives

Current literature presents conflicting evidence regarding the reliability of B-cell aplasia as a marker of CAR-T cell persistence and long-term remission, raising uncertainty about its value. Numerous studies treat the persistence of B-cell aplasia as evidence of ongoing CAR-T cell therapy, associating prolonged aplasia with higher efficacy and lower relapse risk. Contradictingly, others present patients who had persistence of B-cell aplasia, yet still experienced relapse, impugning whether prolonged aplasia is not necessarily directly associated with relapse factors, suggesting the irrelevance of B-cell aplasia markers. Despite its constant use, studies present that some patients who suffer from relapse after the treatment didn't show previous loss of B-cell aplasia, suggesting that the marker could be a suboptimal strategy for

the prediction of weak therapy or relapse (2, 6). While the aforementioned studies provide evidence that calls into question the marker's credibility, it is still recognized in mainstream studies. Contrary to the aplasia-based analysis of the therapy, retrospective cohort studies continue to support the association between prolonged B-cell aplasia and treatment effectiveness. Moreover, these contradictory opinions continue to ignore fractionated dosing despite the influence of B-cell aplasia on clinical dynamics and patients' reliance on the marker.

Socioemotional Aspect of CAR-T Cell Therapy

While CAR-T cell therapy is often discussed from a scientific perspective, a patient and societal perspective is also crucial to revealing and analyzing the treatment's complexities. Regarding CAR-T cell therapy, current literature suggests increased adverse mental health outcomes after receiving treatment. Furthermore, the studies present that patients would often experience stress through both psychological and physical factors, impacting their social functioning and daily life due to their constant fear and impact from both their treatment and their disease (8, 9). Moreover, it examines the full extent of the unpredictability of CAR-T cell therapy. In the context at hand, prior studies suggest that different treatment pathways—each capable of improving cancer outcomes in various ways but also capable of replacing them with other outcomes, such as increased toxicities or a declining immune system (8, 9, 10). Given the wide range of results that contribute to the unpredictability and ambivalence of the treatment, alongside gaps, this sense could continually unsettle patients.

A patient-centered approach to the impacts of CAR-T cell therapy underscores the importance of patients' well-being and societal understanding of the therapy. At the same time, research across fields—such as myeloma and hypertension—highlights the importance of past experiences and opinions in decision-making, examining the high prevalence of three core values: the intensity of side effects, costs, and convenience (11, 12). Although the data is collected from two unrelated studies, both aim to examine common trade-offs. This offers valuable insights into patient preferences and perceptions regarding these trade-offs. Furthermore, although irrelevant to CAR-T cell therapy, they suggest that, across conditions, people often prioritize side-effect burden, cost, and convenience when evaluating treatment options, suggesting the potential value of CAR-T cell therapy to stakeholders. Moreover, despite the aforementioned lack of direct correlation, given that values are influenced by society and subjective opinions, a small population could provide insight into a prevalent mainstream opinion, as Stephens-Davidowitz notes: "The bigger an effect, the fewer the number of observations necessary to see it" (13).

Gaps and Conclusion

In summary, the professional conversation reflects consensus on current research on CAR-T cell therapy, establishing substantial efficacy and the prevalence of toxicity, and explores dose fractionation as a mitigating factor for toxicity, while documenting the psychological burden experienced by treated patients. However, in the context of dose fractionation, no current studies have examined the incidence and severity of B-cell aplasia, nor its reliability as a marker of CAR-T persistence. Moreover, while

existing case studies and qualitative data highlight patient mental health and caregivers, minimal research exhibits the values of benefits and trade-offs of patients, parents, or society, alongside diminished understandings of CAR-T cell therapy. Drawing on current research, this study identifies gaps by examining how parents of Taiwanese high school students perceive regimens of fractionated CAR-T cell therapy that incorporate B-cell aplasia, thereby linking scientific markers and societal perspectives on risks and benefits.

METHODOLOGY

Research Design and Approach

The research adapts a mixed-method approach to examine the patterns of B-cell aplasia tied to CAR-T cell therapy and patient perspectives. Although the study is commonly conducted using a mixed-methods approach that examines patient and human behavior—such as patient data, assessments, and clinical hypotheses—it may be considered unethical to be examined without a medical license. This project aims to generate quantitative data through computational simulations and to present a visual representation of CAR-T cell therapy under split dosing, alongside survey data to assess parents' attitudes and opinions regarding the therapy's benefits and trade-offs. Simultaneously, integrating qualitative data through interviews with professionals to gain insight into current studies and views within the field; however, due to repeatedly failed recruitment attempts, only the survey and simulation data were retrieved. The survey exhibited a Likert scale design, compared to the professional interview questions, which were designed to examine the contrasting opinions and understandings of treatment. Using a mixed-methods design, the study aims to address gaps in the current literature on societal perspectives, focusing on trade-offs, benefits, and overall understanding, while also reconciling contrasting findings on B-cell aplasia.

Computational Simulation

To generate visual data to examine an imitation of B-cell aplasia under different split dosages, single-dosing, and split dosing over 2-3 days (which have been suggested to have different outcomes in the current literature), a computational simulation implemented in Python using the CARTmath framework was developed (4). The simulation used the publicly available CARTmath model implemented in Python (version 3.6), based on the ordinary differential equations described by Barros et al. (14), was selected as it simulates the dynamics of CAR-T cell therapy under specified conditions and quantifies cellular responses (e.g., toxin release) during treatment. Although CARTmath does not directly model B-cell aplasia, cytokine release syndrome, or CAR-T persistence, it serves as a conceptual illustration rather than a clinically validated prediction. The presented simulation utilizes the model's underlying cellular expansions to conceptually address connections to current literature, whereas genetic variation and patient effects were ignored due to the model's limitations.

The simulation variables included (a) initial tumor burden, (b) initial CAR-T cell count, and (c) Cytokine concentration. All simulations were conducted over a fixed horizon time of 200 days (model time). Furthermore, numerical integration was performed using a fourth-order Runge–Kutta method with a time

step of 0.01 days to ensure stability and consistency. When implementing the simulation, initial parameters for CAR-T cell therapy dosage (single dose, three doses) are set, and the model is run, producing numerical outputs to be subsequently plotted. Essentially, the simulation would compare a single dosage input of 2 x 10^6 CAR-T cells/kg on t= 0, then compare to a fractionated dosage delivering the exact dosage across days 42, 49, 56, 63 (0.5 x 10^6 cells/kg t= 0, 0.5 x 10^6 cells/kg t= 42, 49, 56, 63). These specific intervals were chosen within the given simulation framework to model a post-treatment to observe the theoretical plateauing effect on cell populations over an extended time period based on suggestions provided by the original simulation itself for the simulation of split dosages. For each dosing scenario, the model was run 3 times with identical parameter values, and the resulting trajectories were plotted and visually compared. As aforementioned, B-cell aplasia's correspondence to Cytokine Release Syndrome addresses the gap covering the current understanding of how B-cell aplasia responds to split dosages. Moreover, the derived simulation reflects the conceptual model and deepens observers' contextual knowledge by presenting a hypothetical model of the therapeutic benefits and trade-offs that can be integrated into surveys without violating ethical constraints.

Parental Survey

To further address gaps in the current literature, which lack research examining patients', parents', and societal perspectives on the trade-offs and benefits of CAR-T cell therapy, the study focuses on self-reported data from parents to provide subsequent insight into these gaps. Comprehensively, by focusing on parents, the data derived are not merely convenient; they also highlight how adults typically make choices for their children, making their views crucial. The primary data are intended to be collected through an online survey created by Google Forms; eligible participants were adults (≥18 years) who self-identified as parents or guardians of at least one student enrolled in a Taiwanese international high school and who could read Chinese or English. However, the sampling primarily targets Taiwanese parents for convenience and may also reveal a standard societal value among the Taiwanese population. Survey links were distributed via (a) school parent group chats from KCISLK and Dominican International School, (b) cram school parent LINE groups, and (c) personal contacts; all invitations contained the same standardized message—visualized within Appendix A. The survey participants were recruited via online group chats and personal connections, such as school parent group chats, cram schools, and family members, to obtain a more diverse sample of parents in Taiwan. The ideal range for this survey would be 50-75 participants in total to provide a general overview of the small population. The survey comprises 11 questions organized into six sections: a) Demographic Information and Understanding of CAR-T cell therapy (4 questions), b) Overall Risk and Benefit Perception (2 questions), c) Perceptions on B-Cell aplasia Tradeoffs (3 questions), d) Different Scenarios (1 question), e) Values influencing decision making (1 question). As presented, the survey's derived sections assess opinions on trade-offs, benefits, and understanding of CAR-T cell therapy. The Perceptions of Tradeoffs was analyzed with the example question: "If CAR-T cell therapy puts a patient into remission (the decrease or disappearance of the signs and symptoms of cancer) but causes 1-2 years of B-cell aplasia. How acceptable is this?" (1= Completely Unacceptable, 5= Highly acceptable). Additionally, the participants'

understanding of the therapy was established through the question "Before reading through the introduction of this survey, did you understand the basic concepts of CAR-T cell therapy, B-cell aplasia, and split dosing?" (1= I did not understand it at all, 3= I understood completely). The questionnaire includes a consent statement that thoroughly informs participants about the study's purpose, procedures, contributions, and conditions for voluntary participation, and it ensures complete anonymity throughout participation. Furthermore, as noted above, the questionnaire consists solely of yes/no or Likert-scale items, as these items have effectively elicited participants' opinions on the presented statements and have yielded only quantitative data. By incorporating a Likert scale, the survey assesses parents' perceptions of the benefits, risks, and toxicities of treatment, as well as their treatment priorities. Exhibited within Table 1., it integrates how each variable and factor was measured. As aforementioned, the benefits, risks, toxicities, and treatment priorities were presented as factors, quantified on a Likert scale, and selected based on the desired level of agreement/disagreement with the statement. Moreover, the actual survey questions and recruitment email/ notes are listed within Appendix B.

Variable	Description	Measurement Scale
Understanding of CAR-T cell therapy	How well they understand or have heard of CAR-T cell therapy	3-point Likert scale (1= Completely **Do Not** Understand to 3= Completely **Understand**)
Priorities	What parents prioritize within treatments (eg, Benefits and Risks)	5-point Likert scale (1= I strongly prioritize **Risks** to 5= I strongly prioritize **Benefits**)
Acceptability of Trade-offs	How acceptable are specific therapies with their given tradeoffs (eg, recovery [temporary] from Cancer **but** 1-2 years of toxicities)	5-point Likert scale (1= Completely Unacceptable to 5= Highly Acceptable)
Given Scenarios + Opinions of Treatment	Likelihood to choose a therapy under a given scenario (eg, more efficient treatment but could lead to more vicious toxicities)	5-point Likert scale (1= Very Unlikely to 5= Very Likely)
Demographics	Individuals' birth date range	Categorical (eg, <1960)

Table 1. Likert Scale Measurements— Variables, Descriptions, Examples, and Measurement.

Professional Opinions

To derive qualitative data to serve as alignment with parental perceptions, professional opinions could highlight contrasting understandings and perceptions of specific values. The qualitative data derived from a small group of professionals could provide context for findings from the parental survey, serving as a developmental source, whereas the data derived would not be integrated into curated comparative datasets. Thus, identifying possible patterns between professionals and society could foster a deeper understanding of the differing perspectives of patients, society, and professionals. The data sample comprises five professionals who have examined CAR-T cell therapy in their careers, with a focus on the Taiwanese context. Five professionals were sampled based on (a clinical or research experience with CAR‑T therapy or hematologic malignancies, (b practice or research in Taiwan, and (c willingness to participate in a 10–20‑minute interview. Moreover, the interviews would be conducted via Google Meet in English or Mandarin, audio recorded with consent, and summarized with detailed notes. The overall intended structure for the survey is: 1) perceived benefits and risks of CAR-T cell therapy, 2) perceptions on fractionated dosing, 3) opinions on B-cell aplasia as a marker, and 4) understanding of societal perceptions in Taiwan.

Although this study had the initial intent of collecting qualitative data from approximately five professionals with clinical or research experience in CAR‑T cell therapy, repeated recruitment attempts (email invitations and follow‑up messages over a four‑week period) did not yield any confirmed interviews. Thus, the study proceeds with data derived from computational simulation and parental survey, serving the absence of professional input as both a limitation and an objective for future research.

Data Analysis

With regard to the data collected from the three parts of this study—the simulation, the parental opinion data, and the professional insights into this field —the data will be stored in a locked Google Drive folder. The computational simulation produces visual and numerical representations of the tumor under varying doses of CAR-T cell therapy. The data presented from the graphs would be analyzed based solely on results and numerical results that can be derived from examining the graph and patterns presented within the data; no conclusions would be drawn beyond the established trends observed. The survey data, collected using Likert-scale responses, would be categorized and aggregated to generate graphs. The mean and standard deviations derived from the responses could provide an overall summary of the underlying patterns in mainstream values regarding CAR-T cell therapy, B-cell aplasia, toxicities, and split dosages. Simultaneously, response frequencies will show specific patterns and increases in particular values—such as the speed at which the therapy puts patients into remission or the convenience (weekly, daily, hourly checkups). Meanwhile, the analysis presented would examine mainstream or significant parental values across various CAR-T cell therapy factors. Meanwhile, the mean scores and overall distribution of the data indicate the acceptability of single‑dose and split‑dose scenarios, as well as opinions on the benefits and trade-offs of CAR-T cell therapy. Furthermore, demographic differences,

such as age and gender, would be considered in the data but wouldn't be included in the graphs due to the lack of focus.

Ethical Considerations

To maintain the integrity of this project, numerous ethical considerations—such as anonymization, confidentiality, sampling variation, and consent—were addressed during its implementation. With regards to anonymization, the questions within the survey excluded those that could be correlated with identity such as career, child's exact age and school, and medical history; however, for research purposes, the age range of the parents and their gender was documented but participants could answer "prefer not to say" and all the documented gender-age answers would not be disclosed or embedded within a graph. Moreover, participants were thoroughly informed about their contributions to the experiment and were presented with a consent form before being exposed to any questions. In addition to avoiding exposure, the data is stored in a locked Google Drive account accessible only to the experimenters, supervising teachers (only upon request), and the College Board (only upon request)—and the raw data, such as direct survey responses and interview transcripts, will not be published directly. Concurrently, despite the utmost effort to minimize the limitations of this experiment, the small sample size precludes generalization to parents of International High School students in Taiwan. Despite the data providing only a limited perspective on the values of CAR-T cell therapy, B-cell aplasia, and split dosages, due to the limited number of schools, responses, and variation, the data offer a small insight into the significant presence of shared values.

RESULTS AND DISCUSSION

Introduction

While this study originally anticipated presenting a mixed-method dataset comprising computational, professional, and parental evidence of CAR-T cell therapy, due to a lack of responses, only the computational and parental data will be analyzed. Therefore, the study presents a quantitative descriptive study that evaluates subjective opinions within a convenience sample of Taiwanese parents on CAR-T cell therapy-induced B-cell aplasia under split-dose regimens—visualized with a conceptual computational simulation: CARTmath —to identify an indicative value in relation to current social values regarding treatment preferences. The descriptive statistics present a variation of the Likert Scale to identify perspectives on risks and benefits of CAR-T cell therapy, split dosages, and its toxicities. All of which are accompanied by qualitative numerical data, indicating a less intense aplasia of B-cells when enforced with split dosages, and slightly mitigated toxicities. In continuity, the parental survey identified common values and patterns such as emphasizing the importance of remission rates and severity of toxicities, indicating a possible pathway leading into generic values of society. Moreover, the survey also

identified the acceptability of strong and weak toxicities when correlated to fast remission rates, with risk versus benefit analysis as part of this analysis.

Limitations

Prior to further analysis of the computational simulation, supplementary to the survey data, the limitations of this study need to be addressed again. The survey data were randomized to the greatest extent possible; through personal relations, Facebook, and Line Open chats, the findings derived from this survey cannot be generalized to the broader Taiwanese population due to the non-random, convenience sampling method, but it does provide preliminary insights into the values and analysis of CAR-T cell treatment plans when it comes down to risks and benefits. Concurrently, bias may be contaminated within the surveys as a result of the self-report system that is based on subjective opinions; moreover, participants may lie within the reports, as studies have found the presence of deception within surveys. Nevertheless, the derived data provides a preliminary indication of contextual alignment between values among Taiwanese parents who participated in my survey to identify mainstream values regarding risk and benefits when it comes to treatment options, which is consistent with current literature. On the other hand, all computational simulations do not directly represent real-life situations, but rather model them. Consequently, the data used to back the survey findings may be inaccurate because the mathematical model employed for the analysis can only partially replicate the treatment under standard conditions and current research assumptions, highlighting the limitations of the research. Despite these constraints, the quantitative descriptive design of this study cannot establish causality; nonetheless, the integration of Taiwanese parental survey data, corroborated by CARTmath, further supports the understanding of these values.

Descriptive and Background Statistics

With a total of 59 participants, all consented and completed the form, with an overall distribution of 33% female and 67% male, and an age range of 24-64 years. As visualized within Figure 1, the data indicate awareness of CAR-T cell therapy among parents: nearly 60% have never heard of it, while nearly 40% have heard of it or are unsure. This indicates low awareness of CAR-T cell therapy among the general public, which supports both the earlier literature gap and the educational understanding gap regarding current oncological treatments, underscoring the need for awareness. Additionally, this connects to current literature on mental burden, as parents lack a full understanding of the treatment. Their decisions and opinions are based on intuition and personal knowledge, along with professional opinions, which increases the psychological burden due to their lack of field knowledge (14).

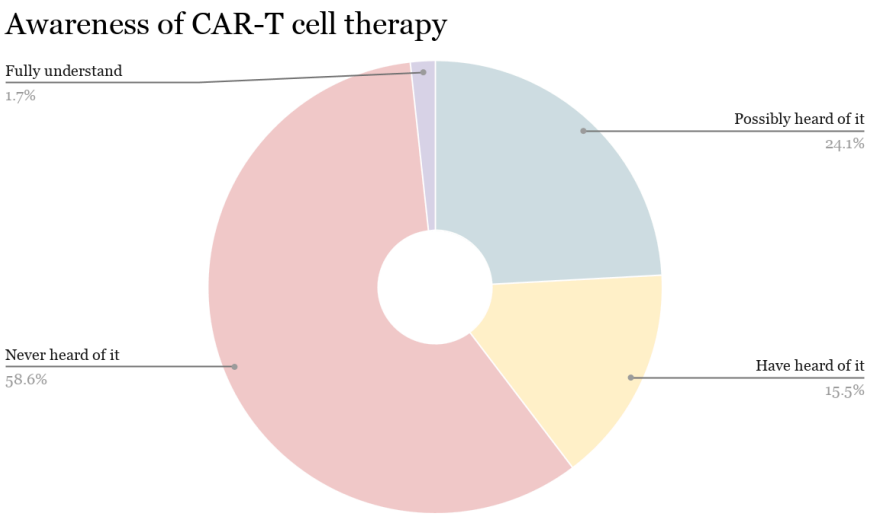

Figure 1. The Awareness of CAR-T cell therapy among parents in Taiwan

Opinionated / Objective Statistics derived from Survey Data

Notwithstanding the limitations, the study offers valuable insights into the mainstream values of Taiwanese parents when faced with risks, benefits, and other treatment factors. In essence, the survey data from Taiwanese parents indicated a strong emphasis on remission rates and the severity of toxicities, paired with a slightly right-skewed bimodal distribution towards risks, suggesting that a large majority of parents prioritize risks, while the rest value both risks and benefits to some extent.

Depicted within Figure 2, excluding the 10% of participants' who responded "I don't know" 44% of the recipients replied to the possible risks of a certain treatment with a considerably negative attitude— "No", "Preferably not"— meanwhile 46% of recipients responded to the selection of treatment with possible risks with a more modest and accepted opinion — "preferably yes", "yes"— showing an overall standard distribution of data. Specifically, a majority of participants selected non-definitive answers when refusing a possible treatment ("preferably not"), reflecting their caution.

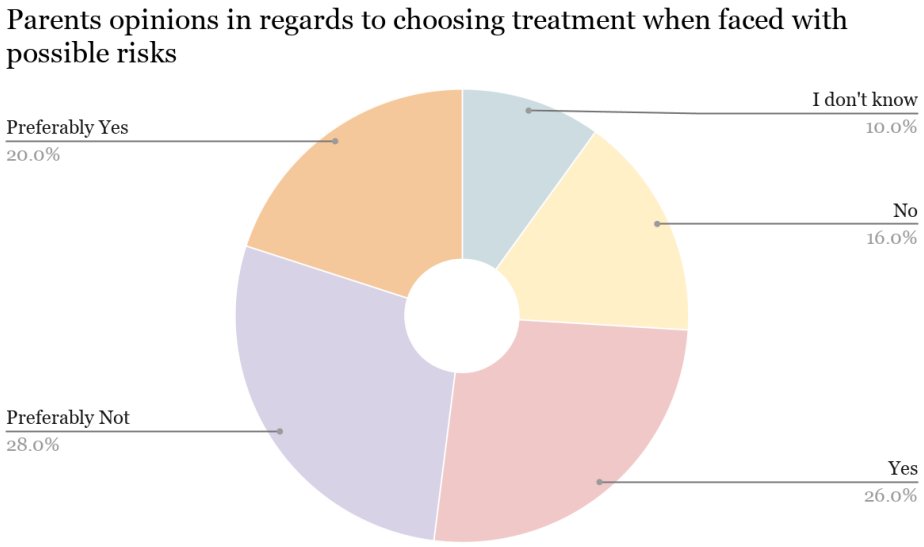

Figure 2. Parents' opinions regarding optimal treatment choice when faced with possible risks

Figure 3 indicates that prolonged durations of CAR-T cell therapy side effects correlate with reduced parental acceptance of the treatment. In response to the prompt regarding B-cell aplasia lasting 1–2 years versus >5 years, the data suggest that parents' acceptability decreases as the period of toxicity lengthens. Consequently, while CAR-T therapy may lead to remission, the long-term prevalence of B-cell aplasia acts as a significant deterrent, shifting some parents toward lower acceptability scores on the 1–5 scale. Moreover, as depicted in Figures 4 and 5, 5 represents prioritizing risks, and 1 represents prioritizing benefits; the graph highlights that the majority of parents value risk assessment most in a treatment. Overall, Figure 4 shows a bimodal distribution that is slightly right-skewed, indicating that although a considerable number of participants remain neutral, there is a pronounced shift toward risk assessment. In addition, the data present the aforementioned bimodal distribution of the risk-benefit question, indicating a strong emphasis on risk relative to the treatment's benefits. Yet, given the suggestive dissociation in the data distribution, this highlights diverse opinions in mainstream decision-making and the difficulty of specifically addressing the top values of parental perspectives, since different parents, when presented with the same things, may choose differently. The presented findings align with the aforementioned literature on Myeloma patients: parents or patients were willing to accept more aggressive treatments for a cure/remission, yet the value of remission decreases as treatments become long-term and have negative impacts, as in both Figure 3 and 4, the toxicities and risks eventually outweigh the benefits (11).

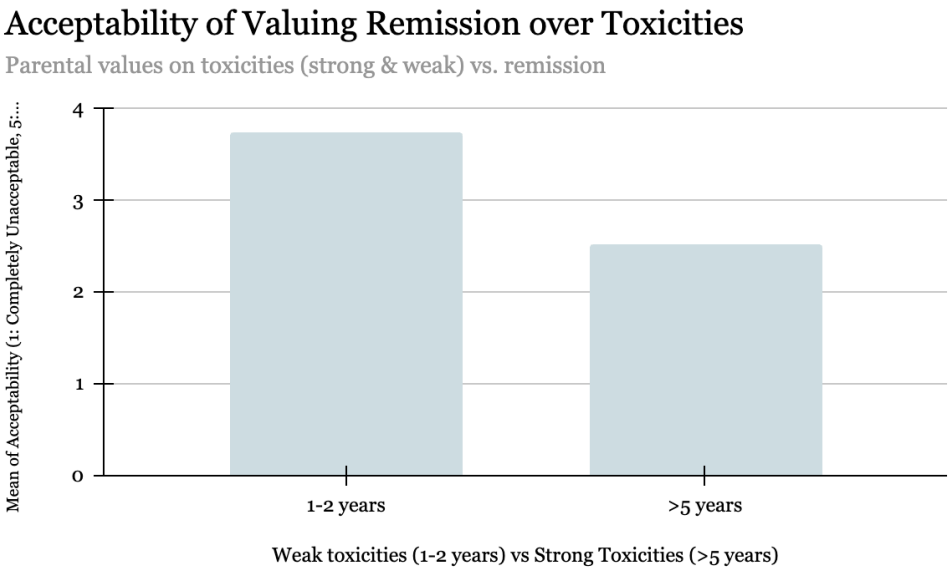

Figure 3. Parental perspectives of valuing remission or toxicities (weak and strong)

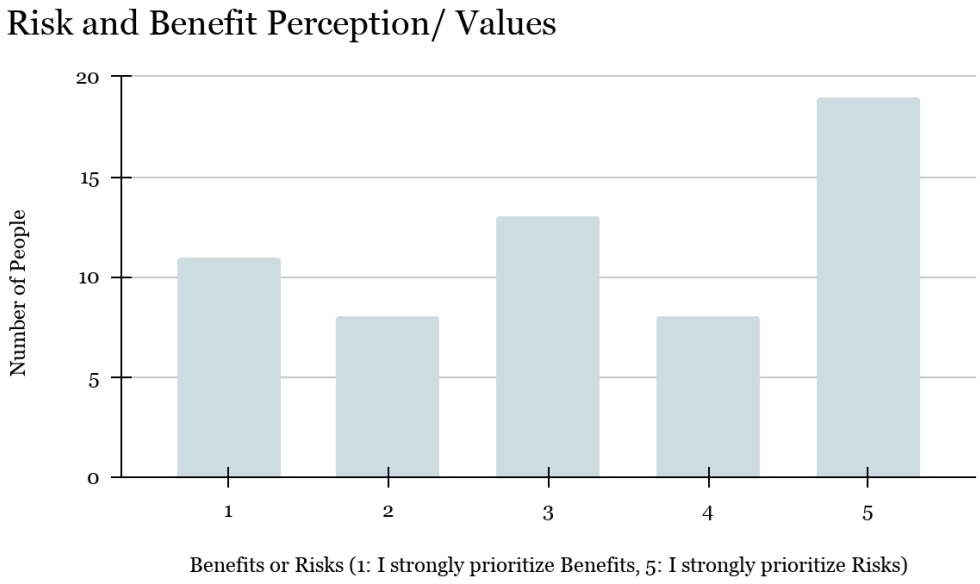

Figure 4. Values regarding Risk and Benefit for Parents

Figure 5 illustrates a 1-5 rating scale, indicating the most and least important values based on subjective opinion. Although participants were not required to rank each factor uniquely, the mean and mode indicate a clear difference. Values with means over 2 are less important, whereas remission rates and

toxicity severity are highly important, with modes of 1 and means under 2. The overlap in modal values—between remission rates and severity of toxicities—suggests a convergence of priorities, indicating that parents value both factors equally. Conversely, logistical factors such as treatment convenience and costs were given lower priority, suggesting that clinical and safety outcomes outweigh practical considerations. Moreover, impact on daily life contributes to a considerably low ranking (mode: 3), depicting the irrelevance of these considerations. These data patterns suggest a possible explanation:when faced with hypothetical scenarios, participating parents may evaluate treatment options through an ethical or health-centric perspective rather than a logistical one, prioritizing health outcomes over anything else. In the context of current literature, this emphasis could potentially be linked to altruistic parental values. A plausible hypothesis for this distribution of values is that because these respondents are not actively experiencing their children going through acute stages of illness and treatment, they may evaluate the trade-offs from a relatively more theoretical standpoint. Supportingly, compared to parents currently experiencing, literature indicates, there is a commonly observed shift in parental perspectives from preserving their children to letting go after witnessing their child endure the physical pain of the treatment (14). Thus, explaining the distribution of values: parents—not experiencing their children going through acute stages of the illness—will value treatments logically—prioritizing remission rates—while the impact on daily life would be a less important factor.

Values influencing decision making	n	mean	mode
remission rates	58	1.81	1
severity toxicities	58	1.689	1
costs	58	2.2758	2
convenience	59	2.1525	2
impact on daily life	58	2.12	3

Figure 5. Rating scale depicting the Most and Least Valued Factors (Scale: 1 = Most Important, 5 = Least Important)

Computational Simulation Results

Figures 6 and 7 exhibit the computational results from the simulation, indicating CAR-T cell expansion and target B-cell aplasia. Within Figure 6, B-cell aplasia (indicated by the red line) occurs instantaneously, visualized by the 90-degree drop simultaneous to the peak of the Effector CAR-T cells. Contrastingly, Figure 7 exhibits a similar but considerably more gradual drop, evident with the less instantaneous drop in cell number. While both figures exhibit total B-cell aplasia, the split dosage model suggests a potentially less aggressive attack and drop towards B-cells, aligning with the parental value of deduced toxicity severity in Figure 5. In correlation, despite split dosages (Fig. 7) having staggered CAR-T cell effector cell release, this doesn't imply weaker treatment efficacy. Moreover, the broader and lower peaks of the Effector CAR-T cells could indicate more plateaued and controlled expansions, which

align with the aforementioned high value for controlling toxicities in Figure 5. Above all, the literature review's gap regarding whether B-cells are a good marker for CAR-T cell therapy is addressed by the presented data, as the rate of depletion can be a potential clinical application to indicate and monitor the efficacy of CAR-T cell therapy.

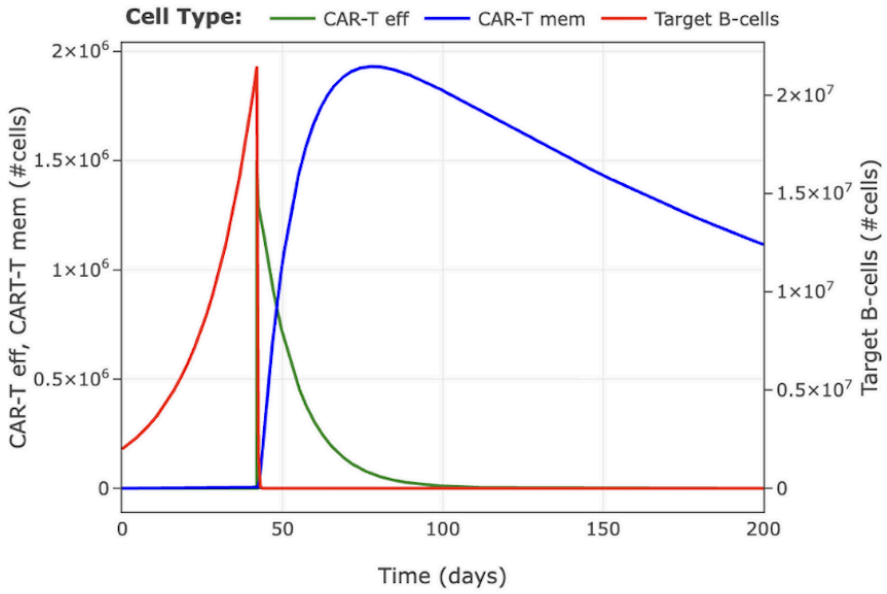

Figure 6. CARTmath Simulation WITHOUT split dosages

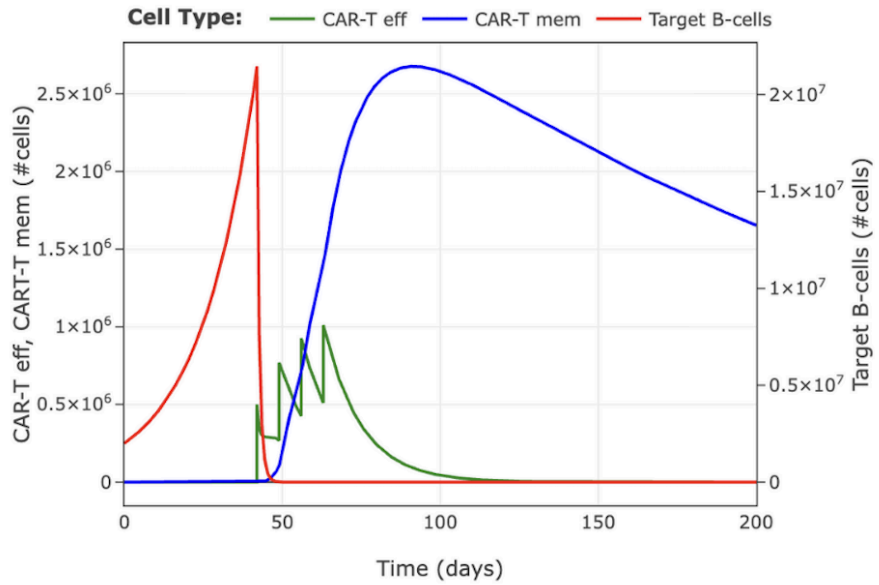

Figure 7. CARTmath simulation WITH split dosages

Future Implications

Despite numerous limitations, the presented data suggest that with consideration of subjective bias, Taiwanese parents tend to prefer and value safety outcomes such as toxicity severity and remission rates over logistical values such as cost and convenience, due to a lack of experience to consider their child's emotional and physical pain. The data, although not directly establishing mainstream values of general Taiwanese society, highlight the significance of valuing safety, such as the elongation of their children's lives and having faster remission rates with reduced toxicities. Moreover, the computational data suggests the B-cell aplasia under split and single dosages, identifying a comparably more plateaued expansion of the therapeutic. Future research could be conducted in numerous regions of Taiwan—as this study focuses mostly on Taipei—to identify a broader and more generalizable value of how parents value treatments. Moreover, future research could be employed in longitudinal designs, including people of different population groups, conducting interviews, or utilizing multiple different simulations, potentially yielding a more diverse and randomized perspective on the treatment, such as a qualitative case study or a mixed methods experiment. In addition, future research could utilize my original methods, this time including professional interviews—something that was revoked due to the lack of respondents—including opinions and comparison to the values caught by professionals and mainstream society. Professionals in the field could examine utilizing the rate of depletion as a marker for the treatment efficacy instead of the concentration, as it has been discredited. Additionally, professionals could incorporate ethical clinical interviews for real patients and stakeholders impacted by this treatment, which avoids subjective bias and misinterpretation of the questions. Given these implications, the study data presented in this quantitative descriptive study could inform research that further examines mainstream values and awareness of CAR-T cell therapy.

CONCLUSION

In conclusion, this quantitative study utilizing computational simulations and surveys highlighted the value of safety principles among Taiwanese parents. Moreover, through an analysis of the survey data, a slightly right-skewed bimodal distribution towards risks suggests a general majority prioritizing risks, while the rest value both risks and benefits to some extent. Additionally, the data revealed that parents prioritized values such as remission rates and severity of toxicities more in a treatment plan compared to factors such as cost and convenience; through further analysis, it represented how parents had the tendency to value the safety and life of their children over logistical values such as costs and convenience, aligning with the literature of doing anything for their child to live longer, unwilling to let go. Moreover, the computational simulation, with ignorance of simulation limitations, identified the possible marker of the velocity of depletion rather than the concentration for CAR-T cell therapy. The data, derived from computations indicating that split-dosing results in a more gradual B-cell depletion, provide justification for the parental preference for dose fractionation in the observed survey data. Despite the presented limitations, the survey and computational simulation data converge to support the commonly valued

factors, suggesting a possible mainstream value among Taiwanese parents. In essence, while the data can not be ensured to have unbiased results, generalized to identify values of the general society worldwide, or used to make definitive conclusions due to methodological and respondent limitations, they do suggest a possible new marker for CAR-T cell therapy, and a generalized value of safety of the children in cancer treatments, particularly remission rates and severity of toxicities. Thus, despite the inability to identify and ensure more generalized values, the data taken away from this quantitative descriptive study ultimately presents the common value of toxicities and remission as a common value agreed upon among Taiwanese parents who participated in this study. Moreover, by combining simulation with the survey, this research demonstrates the feasibility of corroborating multiple quantitative data sources to integrate and examine existing values within the general Taiwanese society while addressing ethical considerations, thereby enabling future integration.

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Appendix A. *Sample Participant Recruitment Email (English version)*

Dear Parents,

My name is **Student Name**, a student at **School/Institution Name**. I am conducting a research study titled "Evaluating the Trade-offs of CAR-T cellTherapy through the Correlation of Societal Perceptions, Split Dosages, and B-cell Aplasia."

As part of this study, I am gathering parents' perspectives in Taiwan on CAR-T cell therapy, a type of cancer treatment. Your input is invaluable in helping us understand how families perceive the risks, benefits, and trade-offs of this therapy, especially in relation to different treatment scenarios such as split dosing and its impact on patient well-being.

You are invited to participate in a short, anonymous online survey that will take approximately 5-10 minutes to complete. The survey is designed for parents or guardians of students enrolled in Taiwanese International high schools and is available in both Chinese and English. Your responses will be kept strictly confidential and used solely for academic purposes.

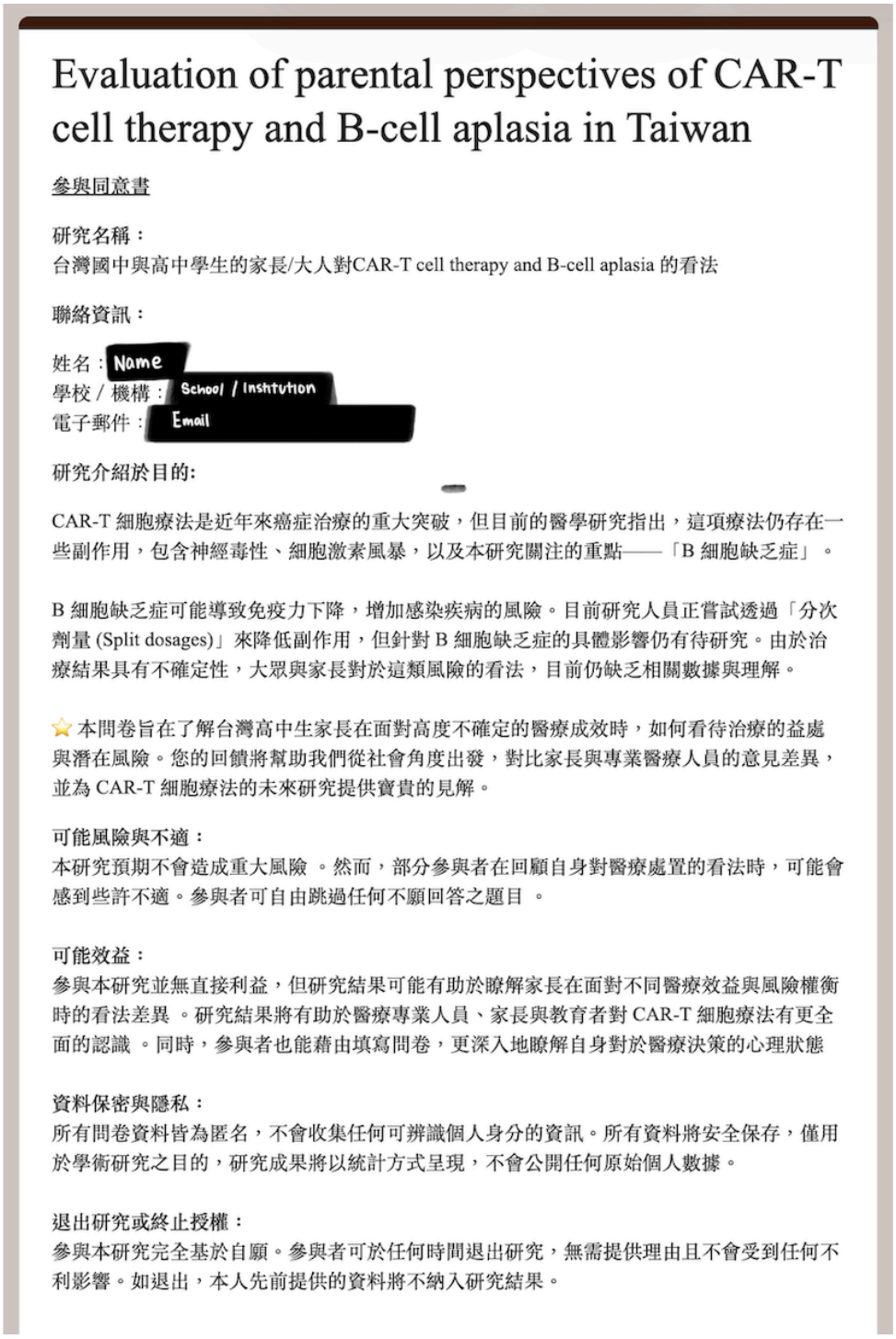
Survey Link: **survey link**

Your participation is entirely voluntary, and you may withdraw at any time. The findings from this survey will contribute to a better understanding of parental perspectives on new cancer therapies and may help inform future educational and healthcare initiatives.

If you have any questions about this research, please feel free to contact me at **Student Email**.

Thank you very much for your time and valuable input.
Sincerely,
Student Name
School/ Institution Name

Appendix B. *Google Form questions and consent for Parental Surveys*



Evaluation of parental perspectives of CAR-T cell therapy and B-cell aplasia in Taiwan

參與同意書

研究名稱：
台灣國中與高中學生的家長/大人對CAR-T cell therapy and B-cell aplasia 的看法

聯絡資訊：

姓名：Name
學校 / 機構：School / Institution
電子郵件：Email

研究介紹於目的:

CAR-T 細胞療法是近年來癌症治療的重大突破，但目前的醫學研究指出，這項療法仍存在一些副作用，包含神經毒性、細胞激素風暴，以及本研究關注的重點——「B 細胞缺乏症」。

B 細胞缺乏症可能導致免疫力下降，增加感染疾病的風險。目前研究人員正嘗試透過「分次劑量 (Split dosages)」來降低副作用，但針對 B 細胞缺乏症的具體影響仍有待研究。由於治療結果具有不確定性，大眾與家長對於這類風險的看法，目前仍缺乏相關數據與理解。

⭐ 本問卷旨在了解台灣高中生家長在面對高度不確定的醫療成效時，如何看待治療的益處與潛在風險。您的回饋將幫助我們從社會角度出發，對比家長與專業醫療人員的意見差異，並為 CAR-T 細胞療法的未來研究提供寶貴的見解。

可能風險與不適：
本研究預期不會造成重大風險 。然而，部分參與者在回顧自身對醫療處置的看法時，可能會感到些許不適。參與者可自由跳過任何不願回答之題目 。

可能效益：
參與本研究並無直接利益，但研究結果可能有助於瞭解家長在面對不同醫療效益與風險權衡時的看法差異 。研究結果將有助於醫療專業人員、家長與教育者對 CAR-T 細胞療法有更全面的認識 。同時，參與者也能藉由填寫問卷，更深入地瞭解自身對於醫療決策的心理狀態

資料保密與隱私：
所有問卷資料皆為匿名，不會收集任何可辨識個人身分的資訊。所有資料將安全保存，僅用於學術研究之目的，研究成果將以統計方式呈現，不會公開任何原始個人數據。

退出研究或終止授權：
參與本研究完全基於自願。參與者可於任何時間退出研究，無需提供理由且不會受到任何不利影響。如退出，本人先前提供的資料將不納入研究結果。

Informed Consent Form:

Research Study Title:
Evaluation of parental perspectives of CAR-T cell therapy and B-cell aplasia in Taiwan

Contact Information:

Name: Name
School: School / Institution
Email: Email

Introduction and Purpose of the Study:

My research question is "When parents of Taiwan high schools are presented with different dosing outcomes of CAR T-cell therapy regarding B-cell aplasia modeled by simulations, how do they evaluate the risk and benefits of tradeoffs, and how do these opinions align with professional opinions?" CAR-T cell therapy for oncological use has been around for a few decades and has become popular in recent years. While work presented by the Nature Review Clinical Oncology states that despite the recent breakthroughs in the treatment of the therapy, humans have yet to find treatment for its toxicities, including neurotoxicity, cytokine release syndrome, and B-cell aplasia. The basis of this research is highly focused on B-cell aplasia, which could possibly result in exposure to diseases and infections. Researchers are also examining "split dosages," which have shown that as the treatment duration is extended with lower doses, toxicities decrease; however, this has yet be examined for B-cell aplasia. These aforementioned factors, along with the lack of predictability of the therapy, create numerous gaps in this topic. Furthermore, research on the societal and parental perspectives on the therapy has also revealed a lack of understanding.

⭐ The purpose of this survey is to understand how parents of high school students in Taiwan perceive the benefits and tradeoffs of Car-T cell therapy, especially considering the differing and unpredictable nature of treatment outcomes. Your response could help me identify patterns in therapeutic perspectives and gain insights into how patients and society would view the trade-offs and benefits of this unpredictable therapy, based on your personal opinions and the information provided. With the addition of a societal perspective and professional alignment, the project could be developed to highlight the relevance of the underresearched topic of CAR-T cell therapy and B-cell aplasia.

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Potential Risks and Discomforts:
There are no significant risks expected. Some participants may feel minor discomfort when reflecting on their perspectives on health treatment. Participants may skip any question they do not wish to answer.

Potential Benefits:
While there is no direct benefit to participants, the study may provide insights into how parents perceive certain benefits and tradeoffs differently. The results may help professionals, parents, and educators better understand CAR-T cell therapy as a whole. Participants can also gain a deeper understanding of their psychological state.

Confidentiality:
All responses will be anonymous. No personally identifiable information will be collected. Data will be stored securely and used only for academic research purposes. No raw data will be presented publicly in the academic paper.

Withdrawal from the Study and/or Withdrawal of Authorization:
Participation is entirely voluntary. Participants may withdraw from the survey at any time without penalty or the need to provide any reasoning. If you choose to withdraw, your responses will not be included in the study.

* Indicates required question

勾選「**我同意**」即表示您確認： *
1. 您已閱讀並理解上述所有資訊。
2. 您自願參與本研究。

By selecting "**I consent,**" you confirm that:
1. You have read and understood the information above.
2. You voluntarily agree to participate.

- ◯ 我同意 I consent
- ◯ 我不同意 I do not consent

CAR-T 細胞療法的背景理解與個人背景。Background understanding of CAR-T cell therapy and Personal Background

您的性別是? What gender do you identify as?

- ◯ 女性 Female
- ◯ 男性 Male
- ◯ 其他 Other
- ◯ 不方便透露 Prefer not to say

您的出生年份是？What year were you born in?

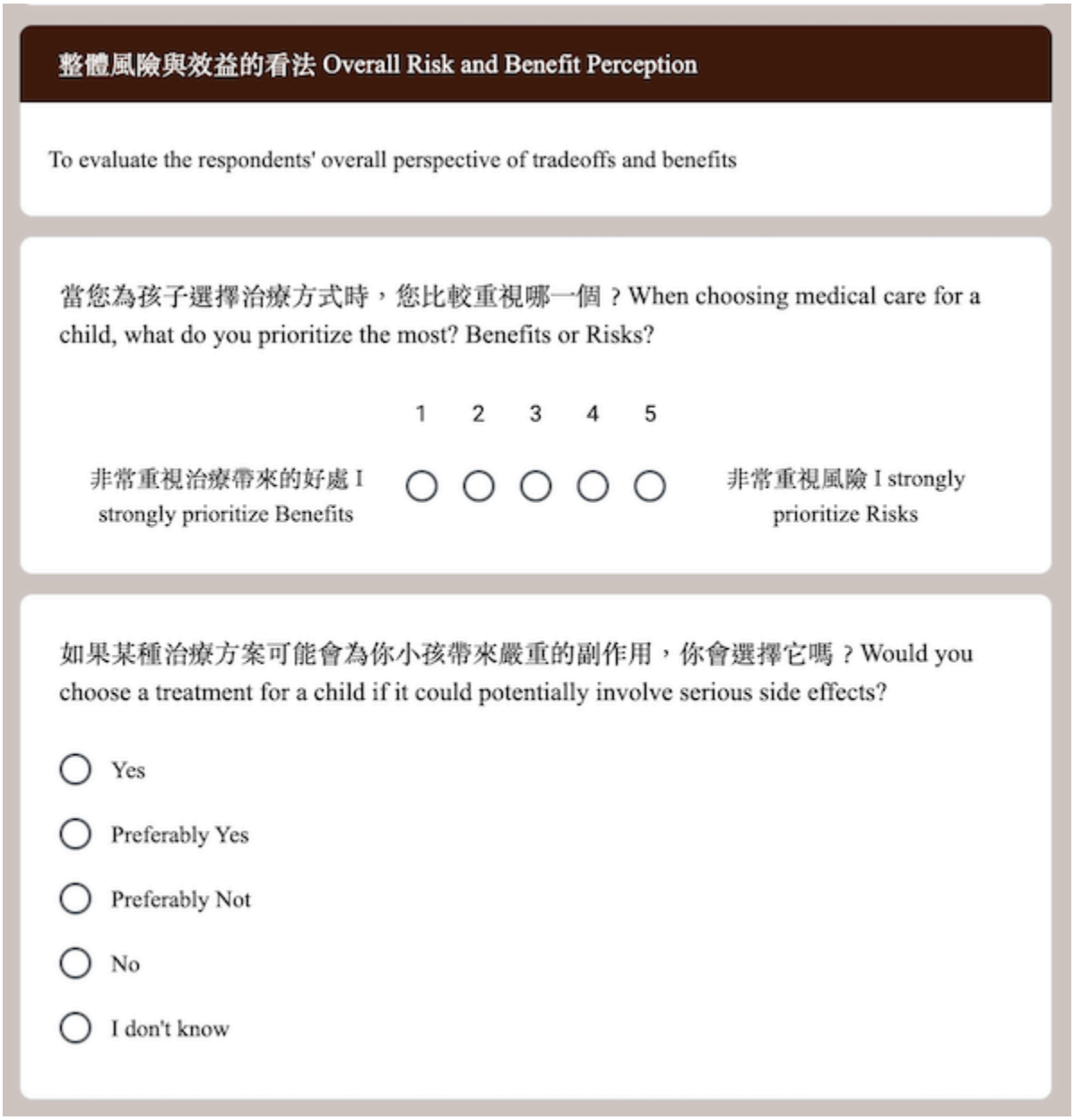
- ◯ <1960
- ◯ 1960-1980
- ◯ 1980-2000
- ◯ >2000
- ◯ 不方便透露 Prefer not to say

在填寫本問卷之前，您是否聽過 CAR-T 細胞療法？Before this survey, had you ever heard of CAR-T cell therapy

- ◯ 從來沒聽過 Never heard of it
- ◯ 可能有聽過 Possibly heard of it
- ◯ 聽過 Have heard of it
- ◯ 聽過且很了解 Have heard of it and fully understand it

在閱讀本問卷的介紹之前，您對以下概念的了解程度是 （CAR-T 細胞療法、B 細胞缺乏症、分次給藥）？ Before reading through the introduction of this survey did you understand the basic concepts of CAR-T cell therapy, B-cell aplasia, and split dosing?

- ◯ 完全了解 I understood completely
- ◯ 大概了解 I understood partially
- ◯ 完全不了解 I did not understand it at all



整體風險與效益的看法 Overall Risk and Benefit Perception

To evaluate the respondents' overall perspective of tradeoffs and benefits

當您為孩子選擇治療方式時，您比較重視哪一個？When choosing medical care for a child, what do you prioritize the most? Benefits or Risks?

	1	2	3	4	5	
非常重視治療帶來的好處 I strongly prioritize Benefits	○	○	○	○	○	非常重視風險 I strongly prioritize Risks

如果某種治療方案可能會為你小孩帶來嚴重的副作用，你會選擇它嗎？Would you choose a treatment for a child if it could potentially involve serious side effects?

- ○ Yes
- ○ Preferably Yes
- ○ Preferably Not
- ○ No
- ○ I don't know

關於 B 細胞缺乏症的取捨看法 Perceptions on B-Cell aplasia Tradeoffs

***說明：以下情境皆為假設情況，主要是為了了解您在不同狀況下的想法，並不代表實際一定會發生。

***提醒：B 細胞缺乏症代表體內的 B 細胞數量非常低，可能會讓患者更容易感染疾病。在最嚴重的情況下，患者可能會因為無法產生足夠抗體，而出現嚴重感染，甚至影響癌症復發的風險（但這種情況並不常見）。

***Disclaimer: these statements and presented situations are fiction to collect an exaggerated version of certain reactions. There is **NO** guarantee that the situation described in the statements will actually occur.

***Reminder: B-cell aplasia is a dangerously low state of B-cells, making the patient increasingly exposed to infections. **Worst case scenario** a patient could suffer from life-threatening infections that could cause the relapse of cancer again because of the lack of ability to make antibodies (but this is unlikely).

如果 CAR-T 細胞療法能讓病人進入緩解期，但會造成 1–2 年的 B 細胞缺乏症，您能接受嗎？ If CAR-T cell therapy puts a patient into remission (the decrease or disappearance of the signs and symptoms of cancer), but causes **1-2 years** of B-cell aplasia. How acceptable is this?

	1	2	3	4	5	
完全不能接受 Completely unacceptable	○	○	○	○	○	非常能接受 Highly acceptable

如果 CAR-T 細胞療法能讓病人進入緩解期，但會造成超過 5 年的 B 細胞缺乏症，您能接受嗎? If CAR-T cell therapy puts a patient into remission (the decrease or disappearance of the signs and symptoms of cancer) but causes **>5 years** of B-cell aplasia. How acceptable is this?

	1	2	3	4	5	
完全不能接受 Completely unacceptable	○	○	○	○	○	非常能接受 Highly acceptable

以下哪一項對您來說最重要？ Which of the following is the most important

- ○ 快速進入進入緩解期 Fast Remission
- ○ 少毒性Less Toxicities
- ○ 兩者都不重要 Neither is important
- ○ 兩者都重要 Both are important

不同情境題 Different Scenarios

以下情境是為了了解您在不同治療選擇下的偏好與價值觀。
過去研究顯示，「分次給藥」可能有助於降低神經毒性與細胞激素風暴，但目前尚未有研究明確說明它對 B 細胞缺乏症的影響。

***免責聲明：由於目前缺乏相關研究，加上 CAR-T 細胞療法本身具有不確定性，以下情境皆為假設推測，並非實際臨床結果。

Different scenarios are presented to the responder to identify common values or certain preferences. Furthermore, as a reminder, split dosages have been shown in past research to mitigate Neurotoxicities and Cytokine Release Syndrome, but B-cell aplasia has not been studied.

**Disclaimer: since the research covering B-cell aplasia is absent, along with the unpredictability of CAR-T cell therapy itself, the simulations are based on mathematical equations, while the outcome could vary in real life.

根據 CARTmath 模擬結果：B 細胞缺乏症與分次給藥的關係

紅線（目標 B 細胞）：
代表體內 B 細胞的數量。當紅線下降到圖表最底部時，表示出現 B 細胞缺乏症。

藍色 / 綠色線（CAR-T 細胞活性）：
代表 CAR-T 細胞在體內的治療濃度與活躍程度。

單次給藥（Single Dosage）：
曲線出現較高、較陡的尖峰，表示治療在一開始對 B 細胞造成較強、較劇烈的影響。

分次給藥（Split Dosages）：
曲線的高峰較低、上升較平緩。雖然模擬結果顯示 B 細胞最後仍可能降到零，但整個過程相對沒有那麼突然、劇烈。

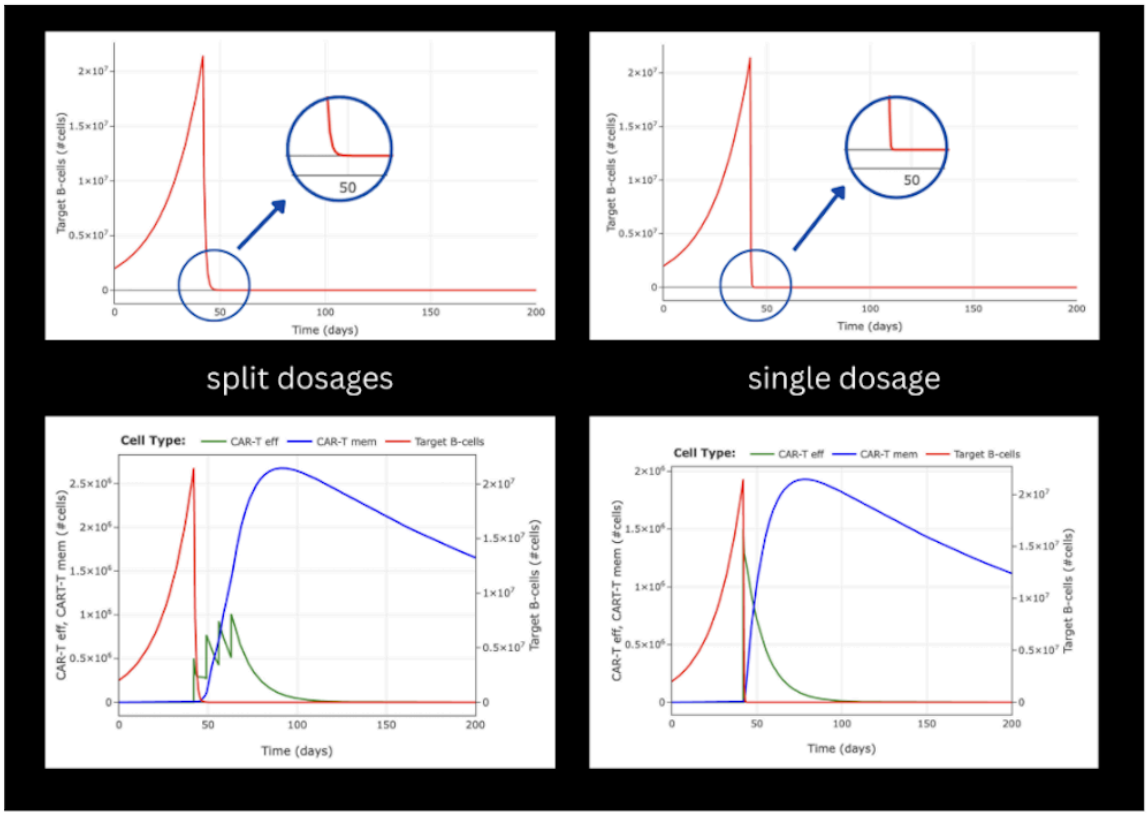
B-cell aplasia's correlation with split dosing based on CARTmath SIMULATION

Red Line (Targeted B-cells): Shows the population of B-cells. A drop to the bottom of the graph indicates the onset of B-cell aplasia

Blue/Green Lines (CAR-T Cell Activity): Show the treatment concentration in the body.

Single Dosage: Shows a **sharper, higher peak**, indicating a more **aggressive** initial **impact** on the B-cells

Split Dosages: Shows lower, more **gradual** peaks. While the B-cells still reach zero, the **simulation suggests the process is less abrupt**



情境一：如果一次給藥的 CAR-T 細胞療法在讓癌症緩解方面效果較好，但副作用也可能更嚴重，您選擇這種治療方式的可能性有多高？ **Scenario 1:** If the CAR-T cell therapy, over a single dosage, could likely be more **efficient** regarding remission but could also lead to **more severe side effects**, how likely would you choose it?

	1	2	3	4	5	
Very Unlikely 非常不可能	○	○	○	○	○	Very Likely 非常可能

Values influencing decision making

當您為孩子決定 CAR-T 細胞療法的治療方式時，以下哪些因素對您來說最重要？（1= 最重要, 5= 最不重要） When deciding treatment plans for CAR-T cell therapy, which are the most important (1= Most Important, 5 = Least Important)

	1	2	3	4	5
治療讓癌症進入緩解期的速度 The speed the therapy puts patients into remission	○	○	○	○	○
副作用 / 毒性的嚴重程度 The severity of the toxicities/ side effects	○	○	○	○	○
治療費用 Costs	○	○	○	○	○
就醫與照護的便利性 Convenience (weekly, daily, hourly check ups)	○	○	○	○	○
對日常生活的影響 Impact on daily life	○	○	○	○	○