Survey Report

Perception Mapping of Indian Physician on Role of Pegaspargase in Management of ALL

Version No.: 1.0

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy, accounting for approximately 25% of all pediatric cancers [1]. In India, the incidence of ALL is estimated to be 9-10 cases per 100,000 children per year, with significant variations across different regions of the country [2]. The management of ALL has seen remarkable progress over the past few decades, with overall survival rates in developed countries now exceeding 90% for children and 75% for adolescents [3].The treatment of ALL typically involves a complex, multi-phase chemotherapy regimen, including induction, consolidation, and maintenance phases. Among the various chemotherapeutic agents used, L-asparaginase has played a crucial role in improving outcomes since its introduction in the 1960s [4]. Pegaspargase, a pegylated form of L-asparaginase, has gained prominence due to its longer half-life and reduced immunogenicity compared to native L-asparaginase [5].

In India, the management of ALL present's unique challenges, including resource constraints, delayed diagnosis, and treatment abandonment [6]. The choice of treatment protocol can vary among centers, with some following international protocols like the Berlin-Frankfurt-Münster (BFM) protocol or its variants, while others may use locally adapted regimens [7]. The use of Pegaspargase in ALL treatment protocols has been associated with improved outcomes, particularly in high-risk patients and those with T-cell ALL [8]. However, the optimal dosing strategy, especially in the context of different risk groups and relapsed disease, remains a subject of ongoing research and debate.

Relapse remains a significant challenge in ALL management, occurring in approximately 15-20% of patients [3]. The approach to relapsed ALL can vary, with options including second-line chemotherapy regimens, immunotherapy, hematopoietic stem cell transplantation, and more recently, CAR-T cell therapy. The role of Pegaspargase in relapsed ALL protocols is an area of active investigation. Given the evolving landscape of ALL treatment and the critical role of Pegaspargase, understanding the current perceptions and practices of Indian physicians is crucial. This survey study aims to map these perceptions across various aspects of ALL

management, including protocol preferences, Pegaspargase dosing strategies, response rates, and approaches to relapsed disease.

2 RATIONALE OF THE STUDY

Managing ALL in India presents challenges due to resource limitations and diverse treatment protocols. While global advancements in ALL treatment exist, their application in India requires careful evaluation. Pegaspargase, an essential part of many regimens, offers potential benefits, yet its optimal use in various patient subgroups and treatment phases remains debated.

This survey aims to align international guidelines with real-world practices in India by mapping physicians' approaches to treatment protocols, dosing strategies, and management of ALL subtypes. Identifying practice variations will inform educational initiatives and refine clinical guidelines, ultimately enhancing patient care. Additionally, the study will investigate strategies for managing relapsed ALL, an area with often suboptimal outcomes, to identify barriers to care and support the development of effective treatment strategies. Overall, the findings will provide a foundation for evidence-based improvements in ALL management, leading to better patient outcomes and more efficient resource use.

3 STUDY OBJECTIVE

To evaluate the perceptions, practices, and treatment strategies of Indian physicians regarding the use of Pegaspargase in the management of ALL.

4 METHODS

This study was a cross-sectional, questionnaire-based survey that aimed to evaluate the perceptions, practices, and treatment strategies of Indian physicians regarding the use of Pegaspargase in the management of ALL. The survey consisted of 15 questions, explored topics such as preferred treatment regimens, response rates for both B-cell and T-cell ALL, total doses of Pegaspargase used, relapse rates, and management strategies for relapsed B-cell ALL. Physicians, including pediatric oncologists, hematologists, and other specialists, were identified and invited to participate through professional networks and medical associations. Participants

were provided with detailed information about the study and gave informed consent before completing the electronically administered questionnaire. Responses were securely stored, and statistical analysis was conducted to identify key trends. The results were compiled into a comprehensive report, with findings intended for publication and/or presentation at relevant conferences. The target sample size for the study was 85 physicians, selected to ensure a diverse and representative sample. Ethical approval was sought from an Independent Ethics Committee, and all participants were assured of their right to withdraw at any time without consequence, with responses anonymized to ensure confidentiality. No treatment was administered, as the study solely focused on collecting physicians' perspectives and practices regarding Pegaspargase use in ALL management.

Data were analysed using descriptive and inferential statistics. Descriptive statistics summarized demographic information and response frequencies. If suitable, inferential statistics, such as chi-square tests or logistic regression, were used to explore associations between physician characteristics and their perceptions and prescribing behaviours.

5 RESULTS

A total of 72 HCPs participated in the survey. Below is the summary of the responses.

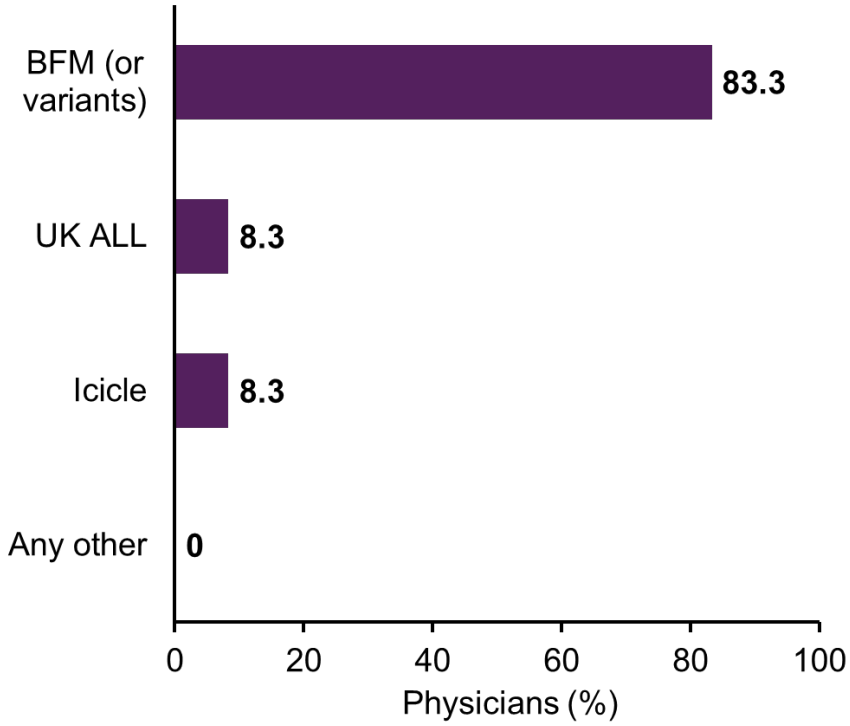
1. In your treatment naïve pediatric patients which regime do you prefer in B cell ALL?

a. BFM (or variants)

b. Icicle

c. UK ALL

d. Any other



- A majority (83.3%) of physicians preferred the BFM (or its variants) regimen for treating treatment-naïve pediatric patients with B-cell ALL.
- Around 8.3% of physicians preferred both the icicle and UK ALL regimen for treating treatment-naïve pediatric patients with B-cell ALL.
- None of the physicians prescribed any other regimen.

2. Above regime is used till what age group?

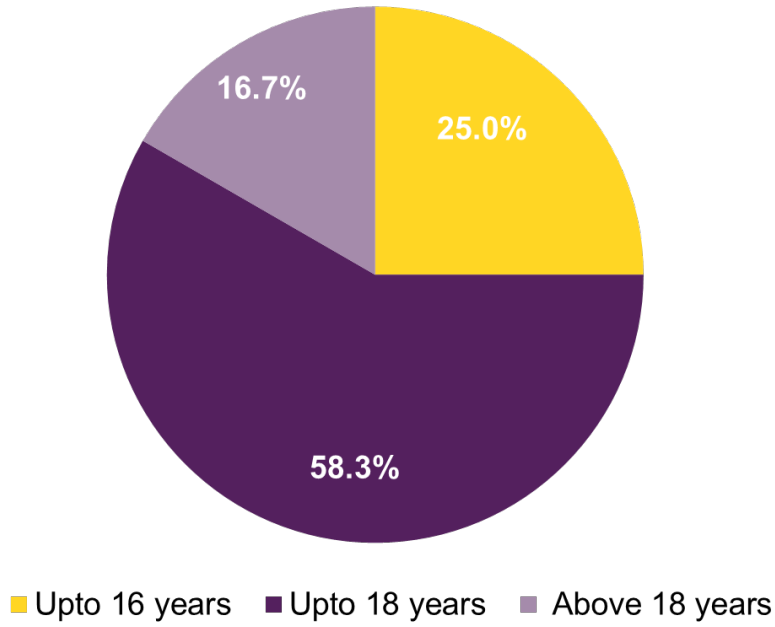
a. Upto 12 years

b. Upto 14 years

c. Upto 16 years

d. Upto 18 years

e. Above 18 years also



- A majority (58.3%) of physicians used the regimen for patients up to 18 years of age.
- Approximately 25.0% of physicians used the regimen up to 16 years of age.
- A small portion (16.7%) of physicians preferred the regimen for patients above 18 years as well.
- None of the physicians used the regimen for upto 12 years and upto 14 years of age.

3. In B cell ALL what is response rates at your center in patients upto 18 years of age?

a. Upto 10%

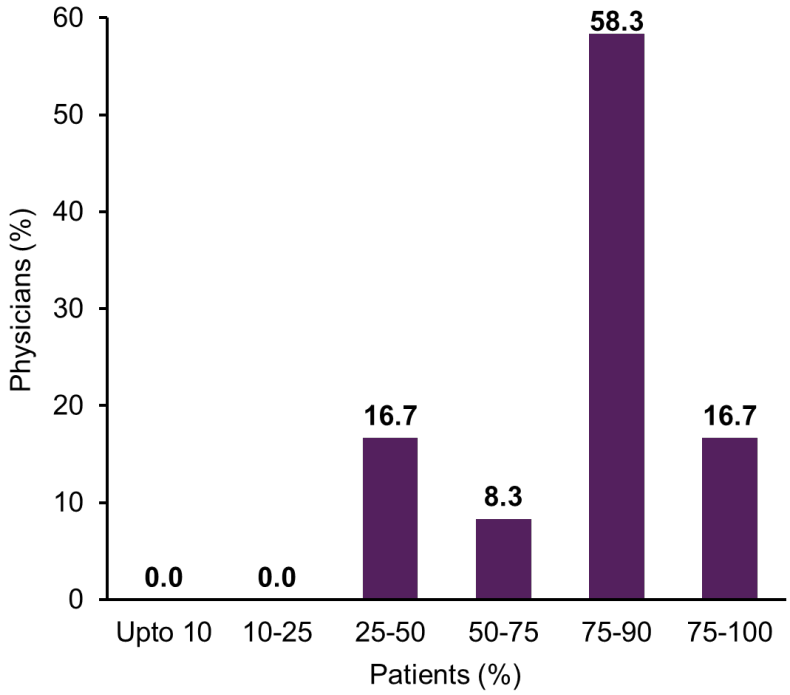
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75 -100%



- The majority (58.3%) of physicians reported a response rate of 75-90% at their center in patient's up to 18 years of age.
- A significant portion (16.7%) of physicians reported a response rate of 75-100%.
- A notable portion (16.7%) of physicians reported a response rate of 25-50%.
- Only a small percentage (8.3%) of physicians reported a response rate of 50-75%.
- None of the physicians reported response rate of 0-25%.

4. In T cell ALL what is response rates at your center in patient's upto 18 years of age?

a. Upto 10%

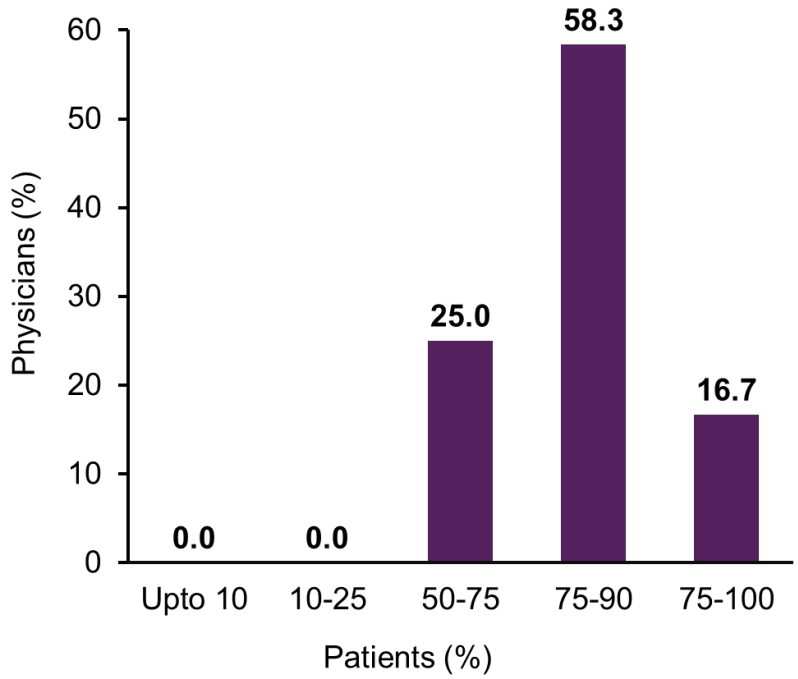
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75 -100%



- The majority (58.3%) of physicians reported a response rate of 75-90% at their center in patient's upto 18 years of age.
- A notable portion (25.0%) of physicians reported a response rate of 50-75% in patient's upto 18 years of age.
- Only a small percentage (16.7%) of physicians reported a response rate of 75-100%.
- None of the physician reported response rate of 0-25%.

5. How many total doses of Pegaspargase are used in both induction and DI phase combined in your patients of B cell ALL (NOT HR)?

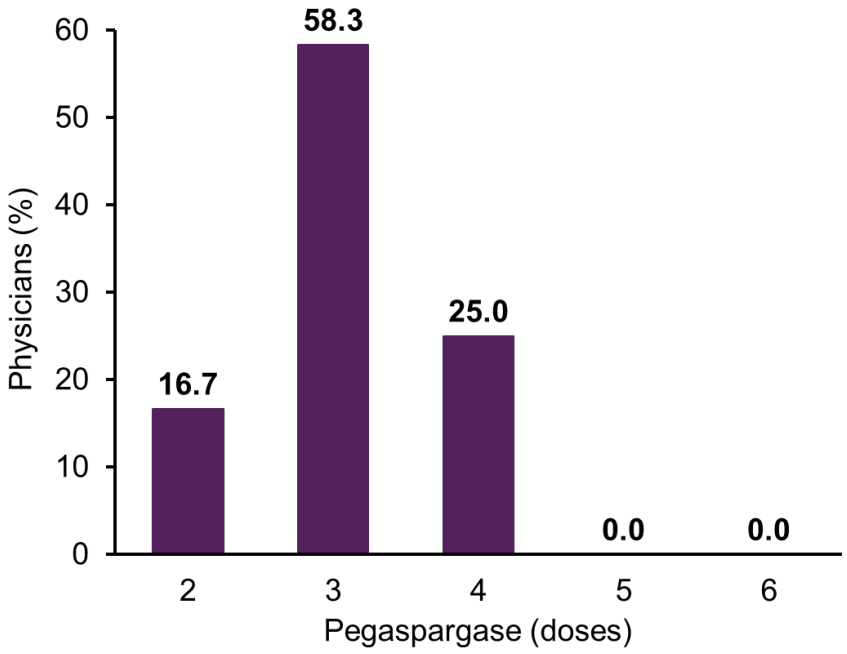
a. 3 doses

b. 2 doses

c. 4 doses

d. 5 doses

e. 6 doses



- The majority (58.3%) of physicians reported using 3 doses of Pegaspargase in both the induction and DI phases for patients with B-cell ALL (non-high risk).
- A smaller portion (25.0%) of physicians indicated that 4 doses are used during these phases.
- Around 16.7% of physicians reported administering 2 doses of Pegaspargase in the combined induction and DI phases.
- No physicians indicated using 5 doses or 6 doses in their treatment protocols.

6. How many total doses of Pegaspargase are used in both induction and DI phase combined in your patients of HR B cell ALL?

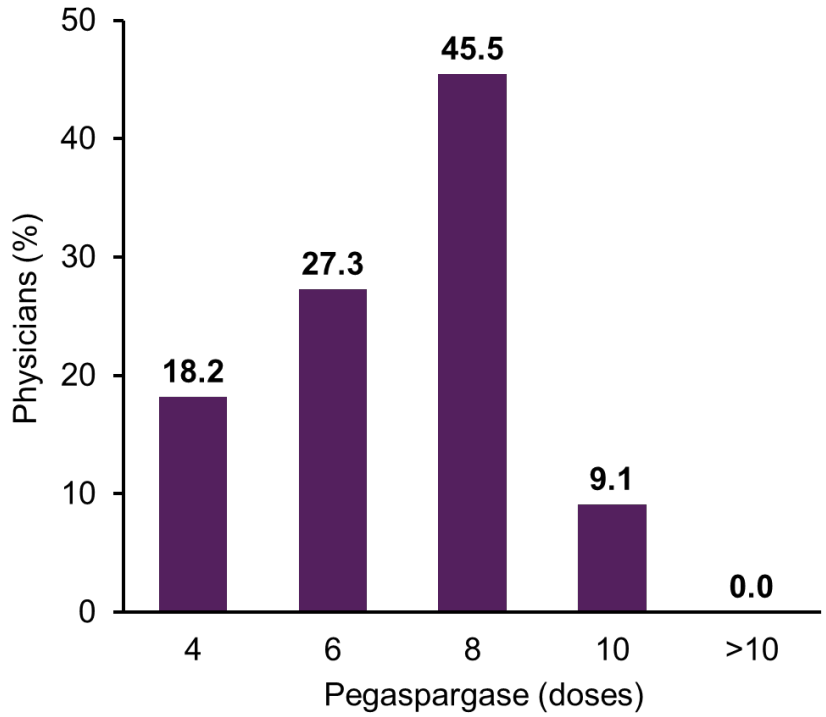
a. 4 doses

b. 6 doses

c. 8 doses

d. 10 doses

e. More than 10 doses



- The majority (45.5%) of physicians reported using 8 doses of Pegaspargase in both the induction and DI phases for patients with high-risk B-cell ALL.
- A significant portion (27.3%) of physicians indicated that 6 doses are used during these phases.
- Approximately 18.2% of physicians reported administering 4 doses of Pegaspargase in the combined induction and DI phases.
- A smaller portion (9.1%) of physicians stated that 10 doses are used in their treatment protocols.
- No physicians indicated using more than 10 doses for these phases.

7. How many total doses of Pegaspargase are used in both induction and DI phase combined in your patients of T cell ALL?

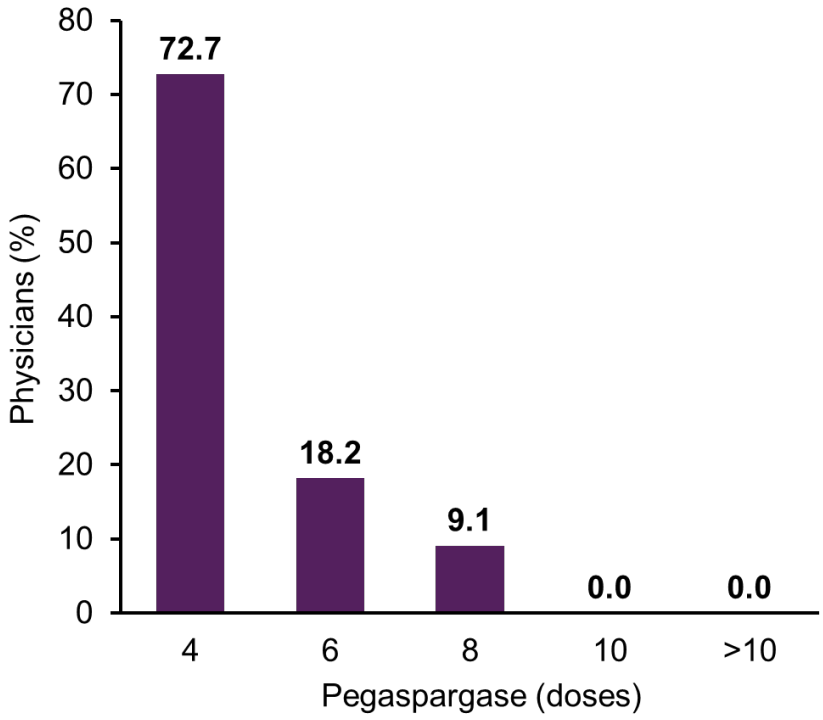
a. 4 doses

b. 6 doses

c. 8 doses

d. 10 doses

e. More than 10 doses



- A majority (72.7%) of physicians reported using 4 doses of Pegaspargase in both the induction and DI phases for patients with high-risk T-cell ALL.
- Around 18.2% of physicians reported using 6 doses of Pegaspargase during these phases.
- While, 9.1% of physicians reported using 8 doses of Pegaspargase in the combined induction and DI phases.
- No physicians indicated using 10 or more than 10 doses for these phases.

8. What percentage your patients relapse in B cell ALL?

a. Upto 10%

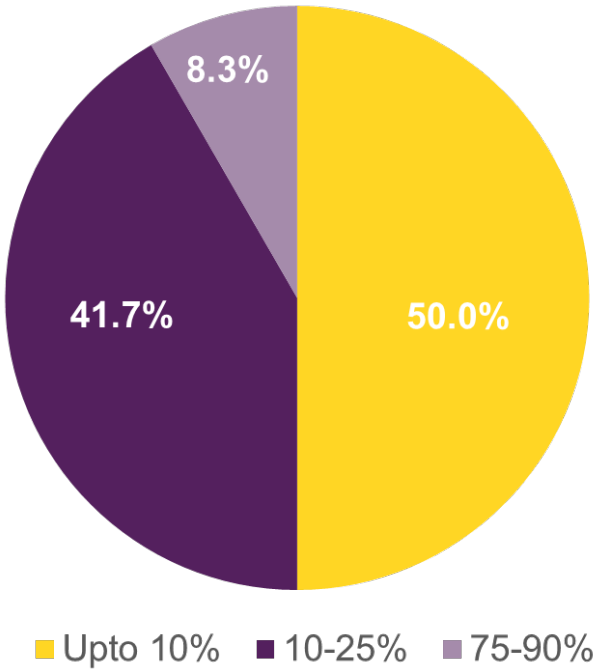
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75-100%



- A majority (50%) of physicians reported that up to 10% of their patient's relapse in B-cell ALL.
- Around 41.7% of physicians reported that 10-25% of their patient's relapse in B-cell ALL.
- A small portion (8.3%) of physicians reported that 75-90% of their patient's relapse in B- cell ALL.

9. What percentage your patients relapse in T cell ALL?

a. Upto 10%

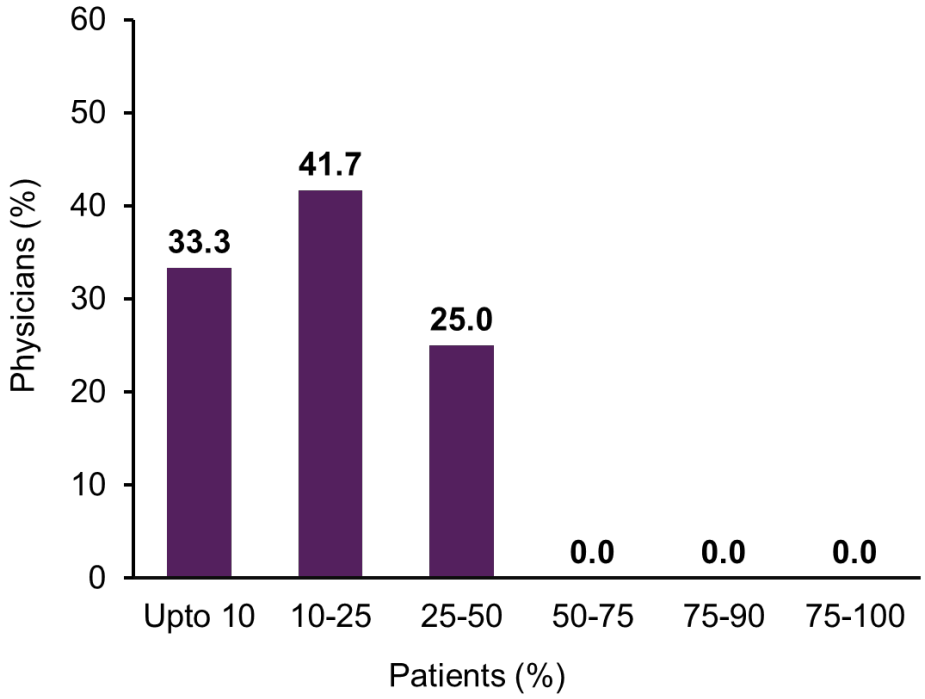
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75-100%



- Around (41.7%) of physicians reported that 10-25% of their patient's relapse in T-cell ALL.
- A notable portion (33.3%) of physicians reported that up to 10% of their patient's relapse in T-cell ALL.
- While, 25.0% of physicians reported that 25-50% of their patient's relapse in T-cell ALL.
- No physicians reported relapse rates higher than 50% for their T-cell ALL patients.

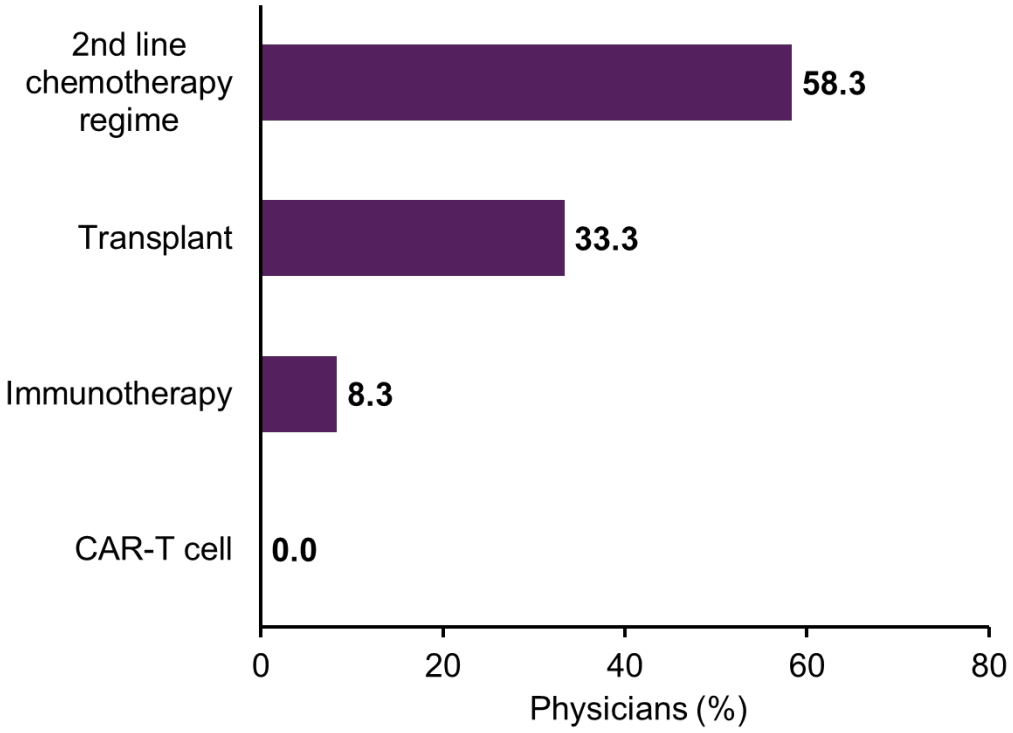
10. Which strategy do you follow in your relapsed B cell ALL?

a. 2nd line chemotherapy regime

b. Immunotherapy

c. Transplant

d. CAR –T cell



- The majority (58.3%) of physicians followed a 2nd line chemotherapy regimen for relapsed B-cell ALL.
- A significant portion (33.3%) of physicians opted for a transplant strategy in the management of relapsed B-cell ALL.
- A smaller group (8.3%) of physicians utilized immunotherapy for relapsed cases of B-cell ALL.
- None of the physician followed CAR-T cell strategy for relapsed B-cell ALL.

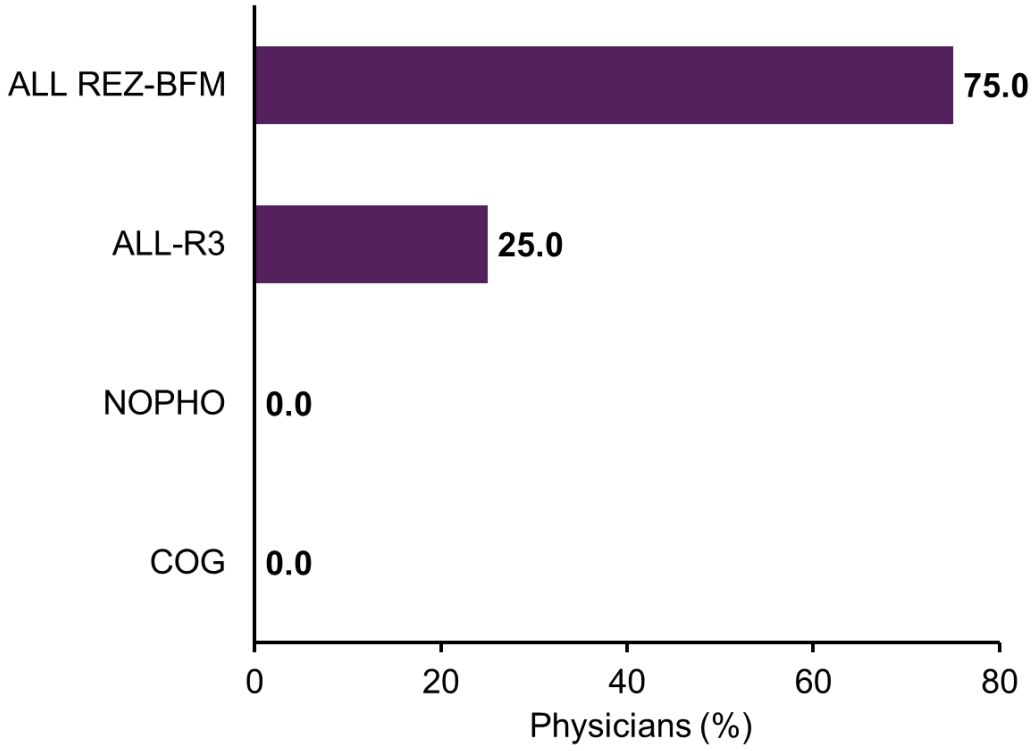
11. Which 2nd line chemotherapy regime you follow in relapsed B cell ALL?

a. ALL-R3

b. ALL REZ-BFM

c. NOPHO

d. COG



- The majority (75%) of physicians followed the ALL REZ-BFM regimen in relapsed B cell ALL.
- While, 25% of physicians followed the ALL-R3 regimen in the management of relapsed B-cell ALL.
- None of the physician followed NOPHO and COG chemotherapy regimen for relapsed B-cell ALL.

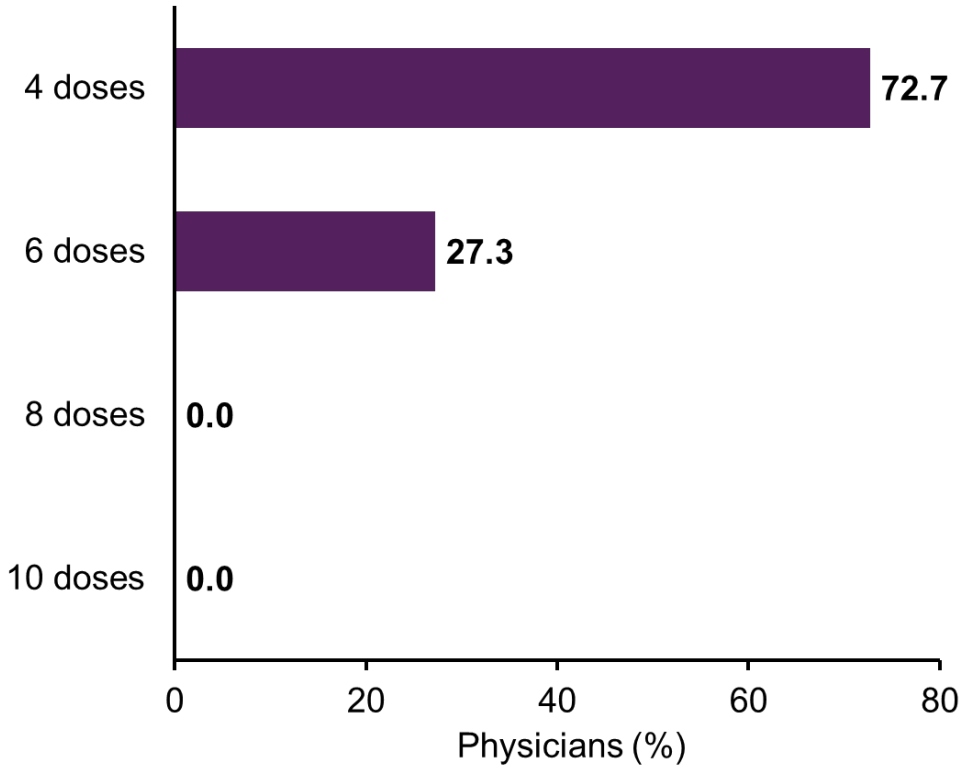
12. How many total doses of relapsed B cell ALL?

a. 4 doses

b. 6 doses

c. 8 doses

d. 10 doses



- The majority (72.7%) of physicians reported using 4 doses for relapsed B-cell ALL in their patients.
- A smaller portion (27.3%) of physicians indicated using 6 doses for relapsed B-cell ALL management.
- None of the physician preferred 8 and 10 doses for the management of relapsed B-cell ALL.

13. How many total doses of Pegaspargase are used in both induction and IM/DI phase combined in your patients of B cell ALL?

a. 3 doses

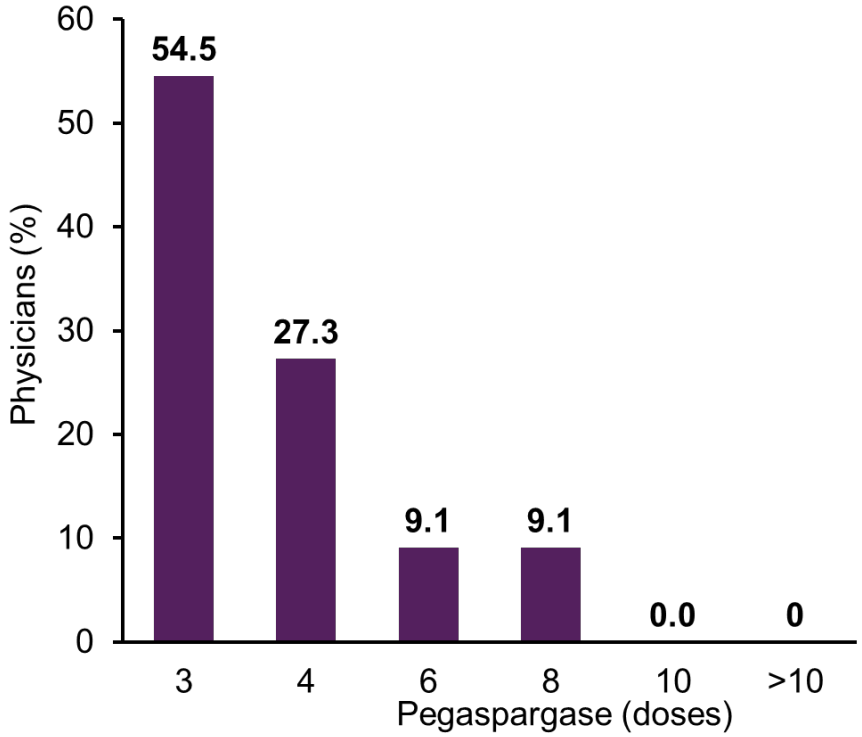
b. 4 doses

c. 6 doses

d. 8 doses

e. 10 doses

f. More than 10 doses



- The majority of physicians (54.5%) used 3 doses of Pegaspargase in both the induction and IM/DI phases for their B-cell ALL patients.
- A significant portion (27.3%) of physicians used 4 doses of Pegaspargase in both the induction and IM/DI phases for their B-cell ALL patients.
- A smaller group (9.1%) of physicians administered 6 doses and 8 doses.
- None of the physicians prescribed 10 or more than 10 doses.

14. In relapsed B cell ALL what is response rates at your center in patient's upto 18 years of age with chemotherapy approach?

a. Upto 10 %

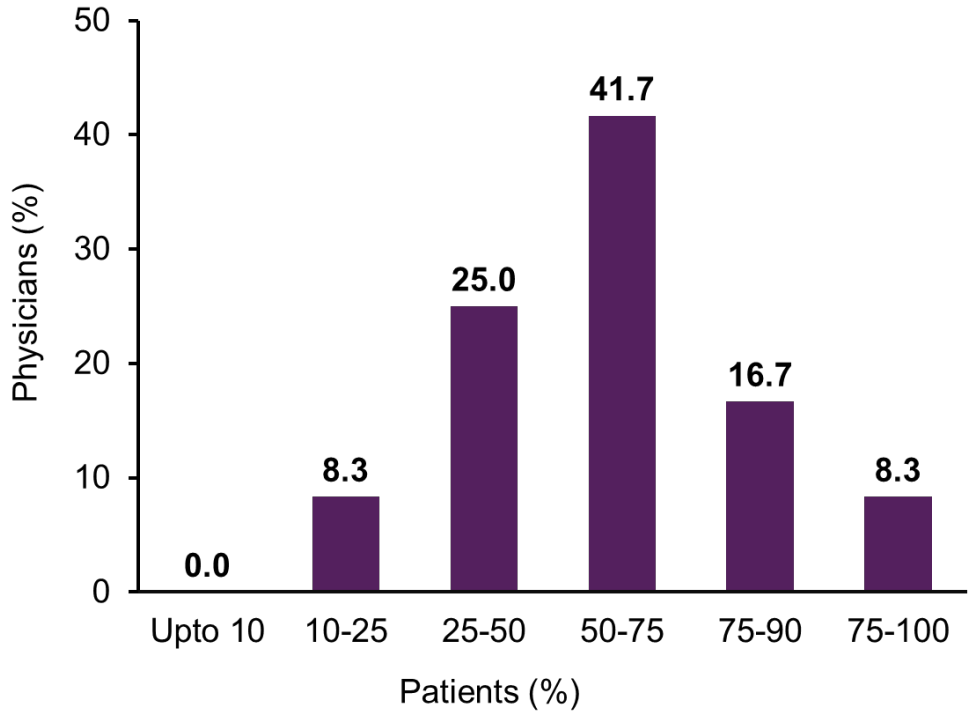
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75-100%



- The majority (41.7%) of physicians reported a response rate of 50-75% in their relapsed B-cell ALL patients (up to 18 years of age) treated with chemotherapy.
- A significant portion (25%) of physicians reported a 25-50% response rate.
- Around 16.7% of physicians reported higher response rate of 75-90%.
- Approximately 8.3% of physicians indicated 10-25% and 75-100% response rates.

15. In relapsed B cell ALL what % of never receive immunotherapy/CAR-T/ Transplant but do receive 2nd line chemotherapy-based regime?

a. Upto 10%

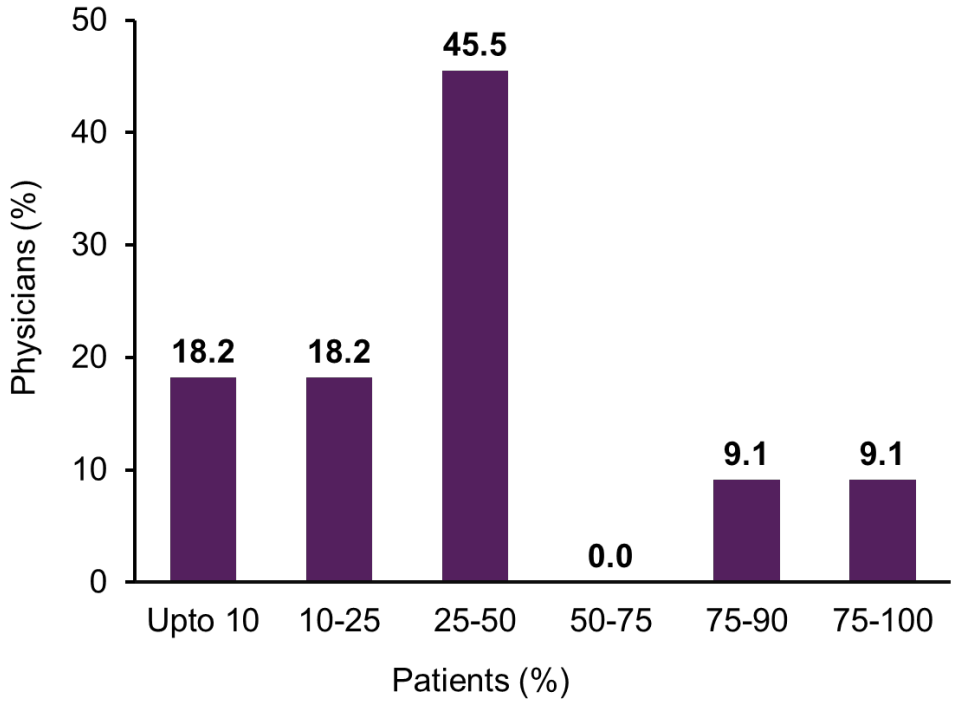
b. 10-25%

c. 25-50%

d. 50-75%

e. 75-90%

f. 75-100%



- The majority (45.5%) of physicians reported that 25-50% of their relapsed B-cell ALL patients, who never received immunotherapy, CAR-T, or a transplant, were treated with a 2nd line chemotherapy-based regimen.
- A significant portion (18.2%) of physicians observed that up to 10% of their patients in this category received 2nd line chemotherapy.

- Around 18.2% of physicians reported that 10-25% of their patients received 2nd line chemotherapy-based treatment.
- Approximately 9.1% of physicians noted that 75-90% of their patients who never received immunotherapy, CAR-T, or transplant, received a 2nd line chemotherapy-based regimen.
- An equal 9.1% of physicians indicated 75-100% of patients received 2nd line chemotherapy in this scenario.

6 SUMMARY

A recent survey of physicians revealed that the BFM regimen (or its variants) is the preferred treatment for treatment-naïve pediatric patients with B-cell ALL, with 83.3% of physicians opting for this approach. Other regimens, such as the Icicle (8.3%) and UK ALL (8.3%) regimens, were less commonly favored. Treatment duration is generally aimed at patients up to 18 years, with 58.3% of physicians following this age group. However, 25% use the regimen for patients up to 16 years, and 16.7% continue treatment for patients above 18 years.

Regarding treatment efficacy, the majority of physicians (58.3%) report a response rate of 75-90%, while 16.7% observe higher responses in the 75-100% range. A smaller proportion of physicians reported lower response rates, with 16.7% noting a 25-50% response, and 8.3% reporting responses in the 50-75% range. When it comes to Pegaspargase dosing, 58.3% use 3 doses, and 25% opt for 4 doses. A minority of physician's report using 2 doses (16.7%) or 6-10 doses (combined 27.3%).

Physicians reported varying relapse rates among patients, with the majority (50%) noting up to 10% of their patients relapse, while 41.7% see 10-25% relapse rates. A smaller group (8.3%) reports 75-90% relapse in their patient population. In response to relapse, most physicians prefer second-line chemotherapy (58.3%), while others turn to transplantation (33.3%) or immunotherapy (8.3%). Additionally, the survey showed that 75% of physicians follow the ALL REZ-BFM regimen, while a smaller group (25%) follows the ALL-R3 regimen, reflecting consistent treatment practices across the board.

7 DISCUSSION

This survey provides valuable insights into the current practices and perceptions of physicians managing pediatric and adult patients with B-cell and T-cell ALL. The data reveals that the majority of physicians favor the BFM (or its variants) regimen for treating treatment-naïve pediatric B-cell ALL, reflecting its strong position in clinical practice. However, a minority of physicians also use regimens such as the Icicle and UK ALL protocols, though these are much less common. The preference for BFM underscores its established efficacy and widespread acceptance, which is reinforced by its high reported response rates in treatment-naïve cases.

In terms of treatment protocols, the survey indicates that physicians predominantly use 3 doses of Pegaspargase during both the induction and maintenance phases for non-high-risk B-cell ALL. A substantial portion of respondents also administer 4 doses, with smaller groups opting for higher doses. Interestingly, for high-risk B-cell ALL, a more varied approach is seen, with Pegaspargase doses ranging from 4 to 8, but no physicians using more than 10 doses. These findings suggest that physicians tend to follow standard treatment regimens, but there is some variation depending on the risk profile of the patient.

For relapsed B-cell ALL, the survey identifies chemotherapy as the most commonly used treatment approach, followed by transplant strategies. A minority of physicians also use immunotherapy, but CAR-T cell therapy is not widely adopted for relapsed cases. In terms of response rates, the majority of physicians report moderate success with chemotherapy, with response rates in the 50-75% range, which reflects the ongoing challenges in managing relapsed disease. Physicians also note a notable portion of patients relapsing within the first few years of treatment, emphasizing the need for more effective strategies and potentially novel therapies.

The survey also highlights significant differences in the management of T-cell ALL compared to B-cell ALL, with Pegaspargase doses in the induction and maintenance phases varying widely among physicians. While the majority follow the ALL REZ-BFM protocol for relapsed B-cell ALL, the ALL-R3 regimen is also reported by some, though less commonly. These results underscore the complexity of treating relapsed ALL, where treatment decisions depend heavily on institutional preferences, available resources, and individual patient factors. The findings of this survey point to

a need for continued research into optimizing treatment regimens, improving response rates, and addressing gaps in current therapeutic approaches, particularly in relapsed cases.

8 CLINICAL RECOMMENDATIONS

- Standardize treatment protocols for pediatric B-cell ALL by continuing to prioritize the BFM regimen or its variants, as it remains the most widely accepted and effective protocol among physicians for treatment-naïve patients. Consider reviewing and optimizing dosing schedules based on the high success rates associated with this regimen.
- Adjust Pegaspargase dosing in both induction and maintenance phases according to risk stratification, with a particular focus on administering 3 or 4 doses for non-high-risk B-cell ALL patients, and 4 to 8 doses for high-risk patients. Close monitoring should be conducted to ensure safety and adjust treatment based on response.
- Refine treatment approaches for relapsed B-cell ALL by prioritizing second-line chemotherapy regimens, as the majority of physicians favor this approach. Explore the potential benefits of incorporating immunotherapy and CAR-T cell therapy in the management of relapsed cases, particularly in patients who fail chemotherapy or transplant options.
- Enhance patient education regarding the potential for relapse in B-cell and T-cell ALL, with a particular focus on managing relapsed cases through second-line chemotherapy or transplant strategies. Educating patients and caregivers about treatment goals and potential outcomes will help manage expectations and improve adherence to treatment protocols.
- Monitor response rates in relapsed B-cell ALL cases, with a focus on the 50-75% response rate observed in the survey. Physicians should be prepared to adjust treatment strategies if response rates fall below expectations, and collaborate with specialists to explore alternative options for patients with poor response to first-line therapies.
- Promote a multidisciplinary approach to the management of relapsed ALL by fostering collaboration between oncologists, hematologists, and transplant specialists. This will ensure comprehensive care for patients who require advanced treatments such as transplant or immunotherapy.

9 CONSULTANT OPINION

The findings from the survey on the management of B-cell and T-cell ALL reflect a clear understanding of current practices and treatment protocols. The widespread preference for the BFM regimen for treatment-naïve pediatric B-cell ALL patients underscores its continued efficacy and reliability, with the majority of physicians acknowledging its success in achieving positive patient outcomes. The variation in the number of doses of Pegaspargase administered during the induction and maintenance phases highlights a personalized approach to therapy, adjusting for both patient risk factors and response to treatment.

The survey results also demonstrate a significant preference for second-line chemotherapy in relapsed B-cell ALL, which remains the mainstay of treatment. However, the growing interest in incorporating immunotherapy and CAR-T cell therapy, especially for patients with relapsed or refractory disease, suggests a shift toward more targeted, precision-based treatments. This progression towards advanced therapies is promising, yet indicates a need for further education and research into optimizing these newer treatment options.

A key takeaway from the survey is the observed relapse rates, with a notable portion of patients experiencing relapse in both B-cell and T-cell ALL, underscoring the need for vigilant long-term monitoring and early intervention. The response rates observed in relapsed cases highlight the importance of customizing treatment regimens based on individual patient responses, with emphasis on second-line chemotherapy and transplant for high-risk patients.

Finally, the survey emphasizes the need for a multidisciplinary approach, with collaboration among hematologists, oncologists, and transplant specialists critical for the successful management of ALL, particularly in relapsed cases. Continuous education and ongoing refinement of treatment protocols will be essential to improve patient outcomes and reduce the burden of ALL in pediatric populations.

10 MARKET OPPORTUNITIES

The survey findings present significant market opportunities for treatment options in both pediatric B-cell ALL and relapsed B-cell ALL. The continued preference for the BFM regimen in treatment-naïve pediatric B-cell ALL suggests a steady demand for products that support this protocol, particularly Pegaspargase. Given that a majority of physicians are using 3 or 4 doses of Pegaspargase during the induction and DI phases, there is a clear opportunity for manufacturers to promote and expand the use of Pegaspargase, especially for high-risk and non-high-risk patients.

In relapsed B-cell ALL, second-line chemotherapy remains the primary strategy, with 58.3% of physicians favoring this approach. However, the growing interest in immunotherapy and CAR-T therapies (albeit at lower frequencies) presents a unique opportunity for biotech and pharmaceutical companies to drive innovation and research in targeted therapies and cellular treatments.

Moreover, the reported response rates, with many physicians seeing 50-75% efficacy in relapsed B-cell ALL, underline the potential for improvements in therapeutic options and treatment protocols. Given the shift towards personalized care and newer modalities, there is an opportunity for companies to introduce new agents or combination therapies that improve response rates and reduce relapse rates, thus enhancing patient outcomes.

Overall, these insights suggest a favorable market environment for both established treatments and emerging therapies, with particular emphasis on educating physicians about new and innovative treatment options for pediatric and relapsed B-cell ALL.

11 MARKET POSITIONING

- A majority (72.7%) of physicians prefer the ALL REZ-BFM regimen for relapsed B-cell ALL treatment, suggesting a strong market for products that support or enhance this protocol.
- With 58.3% of physicians utilizing 2nd line chemotherapy as the primary treatment for relapsed B-cell ALL, there is an opportunity to position chemotherapy agents as the cornerstone of treatment, while highlighting the advantages of new supportive therapies.
- The significant use of 3-4 doses of Pegaspargase in both induction and DI phases for B-cell ALL patients underscores its central role in treatment protocols, creating an opportunity for brands to solidify their position in the market by promoting the clinical benefits of Pegaspargase in this patient group.
- The growing interest in immunotherapy and CAR-T therapies, although currently lower in adoption (8.3% and 0% respectively), highlights the potential for future market expansion in the emerging areas of targeted therapy and cellular treatments.
- The high response rates of 50-75% in relapsed B-cell ALL indicate a need for innovative therapies to improve efficacy and reduce relapse rates. Companies can position their products as enhancing clinical outcomes, especially in relapsed and refractory cases.
- The preference for 2nd line chemotherapy among a significant portion of physicians (58.3%) suggests an opportunity to develop or promote next-generation chemotherapeutic agents that improve response rates and decrease side effects.
- The shift towards personalized treatment regimens for high-risk patients opens avenues for products that can support individualized care strategies and provide tailored solutions to address the specific needs of pediatric and relapsed B-cell ALL patients.

12 REFERENCES

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