v. 5, n. 2, 2025

International Journal of Biological and Natural Sciences

Acceptance date: 20/03/2025

TREATMENT OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA: DRUG INTERACTIONS AND RISK-BENEFIT RELATIONSHIP IN THE BFM AND GBTLI PROTOCOLS

Mailon Santos de Oliveira
Biomedical hematologist - Goiânia (GO)
https://lattes.cnpq.br/1312076311890196

Western Michael da Silva
General Pharmacist, University Center of Goiânia – Uniceug - Goiânia (GO)
https://lattes.cnpq.br/5978480796793268

Larissa de Oliveira Rosa Marques
Specialization student in Medical Genetics and Molecular Biology at the Institute of Health Education and Specialization, IESE - Goiânia (GO)
http://lattes.cnpq.br/8093665238893969

Benedito R. da Silva Neto
PhD Professor who co-supervised the work. Specialist in Genetic Counseling, Master in Molecular Biology, PhD in Tropical Medicine and Public Health
http://lattes.cnpq.br/5082780010357040

Abstract: The treatment of acute lymphoblastic leukemia in children with B and T cells requires specific therapeutic regimens, such as BFM and GBTLI, based on stratified diagnosis according to severity. The objective of the present study was to analyze antineoplastic interactions in relation to safety, the classes employed, and the risks of treatment. A bibliographic review was conducted on specific legislation, books, clinical drug studies, and scientific articles, available in the following databases: LILACS, SCIELO, BIREME, SCIENCE DIRECT, and PUBMED. The beneficial synergistic interactions of daunorubicin, vincristine, prednisolone, and L-asparaginase can be highlighted, as well as antagonistic interactions of vincristine and cytarabine, and cytotoxic effects leading to severe neutropenia, pancreatitis, neural and cardiac cytotoxicity. The BFM protocol obtained a positive response in 70% of cases, compared to 90% positivity with the GBTLI protocol, thus showing that there is a key point between success and failure in treatment, which is the patient's life, and that it requires stratified and accurate diagnosis of the involved cells to guide the best protocol. It is concluded that combined treatment is still the best choice, with positive synergistic interactions in view of the negatives, requiring the use of monoclonal antibodies targeted at remaining malignant cells, based on early diagnosis, corroborating a historical series of success from BFM to GBTLI.
Keywords: Lymphocytic leukemia; Onco-hematologic treatment; Interactions; Treatment; GBTLI; BFM; Synergism; Antagonisms.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) affects 75% of children up to 6 years old and is the most common malignant disease in childhood. It is characterized by the accumulation of precursor B and T lymphoblasts in the bone marrow and lymphoid organs such as the spleen, thymus, and lymph nodes, and may also accumulate in the liver, kidneys, and brain. The cytogenetic and molecular bases of the disease involve chromosomal translocations (t12,21), (p13,q22) caused by the anomalous ETV6-RNX1 protein, which represses the expression of the RNX1 protein, responsible for controlling transcription during hematopoiesis (Hoffbrand; Moss, 2018). However, other studies have shown that not only the ETV-6-RNX1 proteins associated with BCR-ABL1 are sufficient to trigger B-ALL, but also in combination with other anomalous proteins. According to the BFM group, a study conducted with six pediatric ALL patients found variants in IDH1, multi-hit TP53 classified as Li-Fraumeni, KIT, WT1, and fusions such as CBFA2T3-GLIS2, which are associated with the Philadelphia chromosome (Matos et al., 2023; Barbosa et al., 2021).

Childhood ALL with medullary infiltration manifests with anemia, presenting symptoms such as lethargy, pallor, and dyspnea, as well as with neutropenia, leading to fever, malaise, and infections in the mucous membranes, such as the mouth, throat, and skin. It also manifests with thrombocytopenia, especially in the form of bleeding gums and menorrhagia. When affecting organs, it can cause splenomegaly, lymph node enlargement, hepatomegaly, and meningeal involvement. Supportive treatment includes corticosteroids, antimicrobials, hormones, analgesics, antipyretics, and antiemetics, along with specific antineoplastic therapies (Weber et al., 2023). However, before initiating treatment, it is essential to stratify and identify the involved lymphoblastic cells throu-

gh diagnostics such as immunophenotyping, bone marrow biopsy, morphological analysis of blasts in the bone marrow and spinal fluid, peripheral blood analysis, and karyotyping in cytogenetic studies (Boavida, 2021).

With the aim of reducing the number of failed therapies and frequent relapses in the treatment of ALL, the Ministry of Health has decided to consolidate the clinical protocols and therapeutic guidelines (PCDT) with multidisciplinary support. This is based on the Diagnostic and Therapeutic Guidelines (DDT), which are grounded in the best scientific evidence, and involves reformulating both the safety and efficacy of therapeutic regimens, assessing the risk of treatment intensity and the refractoriness of malignant lymphoblasts in the bone marrow. The protocol also highlights the Berlin-Frankfurt-Munich (BFM) therapeutic group from Germany (Brazil, 2014).

However, with the aim of both increasing the survival rate of children undergoing treatment for ALL, which was 70%, and reducing costs associated with the use of non-standardized drugs, a new treatment protocol was created in 2019. This protocol was developed by the Brazilian Group for the Treatment of Acute Lymphoblastic Leukemia (GBTLI), in conjunction with the Brazilian Society of Pediatric Oncology (SOBOPE), and approved by the Medical Ethics Council. The standardization of treatment, following well-defined regimens, has led to an increase in 5-year survival rates from 57% to 90%, according to the Brazilian Association of Lymphomas and Leukemias (Abrale, 2022).

The condition for starting treatment for ALL is the patient's liver and kidney health, as well as the absence of comorbidities. If these conditions are not met, hemodialysis, bone marrow transplantation, and supportive treatment may be necessary. However, if the patient has adequate physiological conditions to receive treatment, it will follow three phases. The first is induction, which aims to preserve normal cells and significantly reduce tumor cells. The second phase is consolidation, which intensifies the treatment of residual cells left over from the previous phase, with the addition of other drugs, such as methotrexate (MTX), for systemic distribution and organ preservation. The third phase is maintenance, which aims to prevent disease relapse and early-stage remission, while minimizing harmful and vesicant effects, always assessing the risk for each patient (Weber et al., 2023).

Therefore, the aim of this study is to analyze and differentiate the risk interactions and the frequency of interactions reported in the literature for the BFM and GBTLI protocols related to antineoplastic treatment in pediatric acute lymphoblastic leukemia. Additionally, the study aims to evaluate the risk-benefit ratio of these protocols and the classes of antineoplastic agents used.

METHOD

A bibliographic review was conducted using books and articles from national and international scientific journals and magazines available in the following databases: LILACS, SCIELO, BIREME, SCIENCE DIRECT, and PUBMED. Relevant information was extracted, including the types of treatments used, study methodologies, sample sizes, significant statistical data, as well as side effects, notable interactions, and treatment outcomes observed in each protocol. Additionally, the review included suggested practices for selecting the best protocol, with the aim of improving patients' life expectancy and ensuring a satisfactory recovery.

Thus, the inclusion criteria for the study comprised the subject matter, selection of national and international journals published between 2018 and 2023, with the exception of resolutions, laws, and protocols created prior

to that period. The treatments analyzed were exclusively focused on children aged 1 to 12, with an emphasis on antineoplastic therapy. Articles not available in full were excluded, as well as studies on palliative care, radiological treatments, and non-antineoplastic therapies.

Finally, the information was analyzed using statistical data related to the general and specific objectives of the study, highlighting the advantages and success rates of the treatments. The discussion addressed the protocols used in antineoplastic treatment, demonstrating that these protocols have established a standard not only for professionals in the Unified Health System but also for the private sector, promoting the rational use of antineoplastic drugs in Brazil and globally, with fewer harmful effects on treated patients.

RESULTADOS E DISCUSSÃO

INTERAÇÕES ANTINEOPLÁSICA APRESENTADO NOS PROTOCOLOS BFM E GBTLI

During clinical studies, it was observed that Daunorubicin, a cytotoxic antibiotic, when used in combination with other antimetabolite cytostatic agents such as cytarabine and cyclophosphamide, can potentiate toxic effects, including bone marrow myelosuppression, gastrointestinal complications, and severe cardiotoxic effects (Wyeth, 2018). This explains why these drugs are not used together in the BFM protocol but are used in the GBTLI protocol. However, these effects can be mitigated by the standard use of prednisolone, a glucocorticoid, to reduce inflammation (Merck Sharp & Dohme, 2021). L-asparaginase, used in both protocols, when combined with the daunorubicin and vincristine complex, can cause severe leukopenia and uric acid accumulation in the body. Some protocols have used glucocorticoids, such as prednisolone and dexamethasone, either alone or in combination, to mitigate the cytotoxic and vesicant effects, which are more pronounced in the GBTLI protocol.This result has been observed in clinical studies, showing that L-asparaginase, when administered after methotrexate and cytarabine, enhances its action, unlike vincristine, which should not be combined with cyclophosphamide due to the risk of severe anaphylaxis and inhibition of its effects when used together. Dexamethasone was incorporated into the GBTLI protocol to reduce inflammation during the induction and consolidation phases (Baxalta, 2016).

In addition, a routine study on the treatment of ALL using the BFM protocol observed interactions between vincristine and cytarabine, which blocked the response of both drugs, increasing disease resistance with hypercalcemia and bone lesions 28 days after the induction phase. However, the empirical interaction between venetoclax, an antimetabolite of the Bcl2 protein, and blinatumomab, a monoclonal antibody that blocks the protein encoded by the TCF3 gene involved in the genetic mutation of T-cell ALL, yielded good results, with hematological remission in the same phase (Oliveira et al., 2022). For these reasons, the BFM protocol recommends vincristine in combination with daunorubicin, prednisolone, and L-asparaginase, which enhances treatment effectiveness during this phase.

On the other hand, despite studies being conducted empirically, cytarabine is used in a second treatment regimen with etoposide in the consolidation phase, to avoid neutralizing vincristine, which is used in the consolidation phase (Brasil, 2024). However, etoposide, being a cytotoxic antibiotic, can potentiate the action of cytarabine according to clinical studies, causing premature bone marrow depression, and is used in second order in consolidation, indicated according to the therapeutic regimen established by the GBTLI group (Blau, 2019).

This fact reveals why cytarabine, methotrexate and cyclophosphamide are not used together in the BFM protocol, despite the risks of cardiotoxicity and hepatotoxicity due to synergistic potentiation in cytotoxic action, these substances are used according to the GBTLI group as a last-ditch attack in severe cases of lymphoblast refractoriness, in combination with 6-mercaptopurine and cytarabine in the MADIT complex, which includes methotrexate, dexamethasone and cytarabine (Correia et al. , 2021; Baxter, 2021).

In clinical studies, 6-mercaptopurine, a pro-drug, was antagonized by methotrexate. This is due to binding to plasma proteins, reducing the transport and metabolization of 6-mercaptopurine, which needs to pass through the 1st order to be activated in the body, and is not indicated together. However, isolated and sequential administration of both is recommended, with 6-mercaptopurine in the first cycle and methotrexate as intrathecal prevention of neural lymphocytic cells (Blay, 2023; Aspen, 2021).

In addition, in clinical studies to prove the efficacy of vincristine under the name Fauldvincri, severe bone marrow depression was observed when administered together with daunorubicin and prednisone, due to the synergism of daunorubicin, so the prescribing doctor should analyze the best course of treatment. However, when used with bleomycin, a cytotoxic antibiotic, its action was easier (Libbs, 2014). The benefit may be greater compared to the damage to the bone marrow because, considering the very narrow therapeutic range of antineoplastics in general, bone marrow transplantation is routine in cases of severe bone marrow depression, as part of the therapeutic protocols used in ALL.

In the treatment according to the BFM group, improvement was observed in 81% of cases in 11 children with B-cell ALL, with relapse in only two after treatment in induction and consolidation. Blinatumomab has been a bet on monoclonal antibodies, with positive results alongside conventional chemotherapy; however, it has proved to be a problem for monitoring the minimal residual disease (MRD) of cells expressing the CD19 and CD22 antigens, and it is not possible to obtain a reliable result of this count (Pontes, 2023). The same was observed in another study, in which substantial improvements were shown with the application of blinatumomab after chemotherapy treatment, especially in T-cell precursor ALL, due to the high expression after intensive chemotherapy in the induction phase (Lagua et al., 2023).

So this shows us that the BFM group's protocol has been adapted with empirical tests to reduce the chemotherapy load, with a reduction in adverse and side effects and greater treatment efficacy, such as the inclusion of monoclonal antibodies. However, in a treatment according to the GBTLI 2009 protocol, with the use of blinatumomab at the start of induction interspersed with inotuzumab at the end, good results were obtained in the expression of CD22 antigens, expressing CD19 soon after the start, allowing total remission of type B leukemic cells. These findings show a total dependence on normal cells for the activation of leukemic cells throughout the induction phase and the beginning of consolidation, allowing the tracking and destruction of tumor cells and a positive treatment (Domingues et al., 2021).

In another study, using the BFM protocol, it was shown that cyclophosphamide, 6-mercaptopurine and cytarabine, when administered in the same cycle, can considerably reduce minimal residual disease, masking the post--induction results (Khandelwal et al., 2023). This result shows us that the drugs work in synergy, effectively attacking cancer cells. Ifosfamide, which is used for maintenance in the GBTLI group due to its analogy with cy-

clophosphamide, should only be used in cases of resistance to consolidation phase cycles, due to its bone marrow depressant effects and neurotoxicity (Eurofarma, 2021).

Finally, according to the GBTLI group, as a result of the longer treatment time, around 90 days, using greater combinations of antineoplastics with total, partial or antagonistic synergistic effects in different drugs, including antimetabolites and inhibitors of proteins essential to the survival of the malignant cell, the daunorubicin, vincristine and L-asparaginase group were the most likely to generate serious adverse effects, but with good results for the treatment. The modulation of the intensity of treatment are factors that are not controllable in the protocol according to the BFM group, but are fully controlled in the GBTLI protocol. However, the use of corticosteroids such as dexamethasone achieved good results in terms of adverse effects, reducing the patient's suffering during treatment, regardless of the degree of involvement of the malignant cells. However, the protocol according to the BFM group is necessary, with better results in the short term. As it is a question of reducing unwanted effects and the benefits of treatment in the risk-benefit binomial, the use of monoclonal antibodies such as blinatumomab and inotuzumab, according to the GBTLI or BFM protocols, is necessary for tracking malignant cells at different stages, in order to monitor the synergistic harmful or beneficial effects of treatment.

ANTINEOPLASTIC CLASSES INVOLVED IN BOTH PROTOCOLS

According to the standard protocol (according to the 2009 BFM group), the use of daunorubicin and vincristine, cytotoxic antibiotics that inhibit the cell cycle in mitosis, is recommended in the induction phase of childhood ALL, as well as corticosteroids, both prednisolone, to reduce inflammation caused by the accumulation of metabolites in the body, and L-asparaginase, a potent inhibitor of cell protein synthesis and, consequently, cell division. However, an additional dose of daunorubicin can be administered (Brasil, 2014; Hoffbrand; Moss, 2018). At this stage, studies have shown relapses with death in 10% of treated patients at high risk for ALL, due to the involvement of lymphoblastic cells with chromosomal tetraploidies and other infectious conditions, such as hemophagocytic lymphohistiocytosis. In the study, the rate of resistance to treatment was measured at 2.10 (95%), according to the established risk diagram, with a range of 1.64 to 2.69. These results were due to severe neutropenia and leukopenia, as well as hematic toxicity and potentiation of the effect of daunorubicin combined with other cytotoxic agents that inhibit protein synthesis, such as vincristine and L-asparaginase, respectively (Ceppi et al., 2022).

The GBTLI protocol presents a more intensive treatment approach for ALL, requiring the analysis of risk factors for patients and stratifying them into low, medium, and high risk categories. High-risk factors include age < 1 year, leukocyte count > 50,000/mm^3, response to treatment after 7 days, and blast infiltration in the bone marrow > 25% within 14 days of treatment. As early as the induction phase, glucocorticoids such as dexamethasone are introduced in the first few days, along with cytotoxic antibiotics such as vincristine and daunorubicin (an agent that inhibits the synthesis of cell cycle proteins), L-asparaginase, and a combination of antimetabolites like methotrexate and cytarabine. Glucocorticoids like dexamethasone are also used to manage the inflammation caused by these drugs (Correa et al., 2021; Hoffbrand & Moss, 2018).

The combination proposed by the GBTLI group requires a longer treatment duration, around 60 days for the induction phase, due to the broader range of antineoplastics used. This includes the substitution of the second dose

of daunorubicin with cytarabine, a deoxyribonucleic acid inhibitor that interferes with early cell cycle maintenance, and the replacement of prednisolone with dexamethasone to enhance the reduction of inflammation. These changes demonstrate a strategic approach to expanding pathways for inhibiting the growth of lymphoblastic cells in this protocol.

The consolidation phase in the GBTLI group also differs due to the greater variability of chemotherapy compared to the BFM group. Four cycles of daunorubicin, vincristine, oral prednisolone, and L-asparaginase are administered in double doses on days 2, 4, 7, 9, 11, and 14, followed by a second regimen consisting of cytarabine combined with another cytotoxic antibiotic, etoposide, on days 1, 4, 8, and 11 of the same phase. Intrathecal prophylaxis with six doses of methotrexate is included throughout induction, during the first consolidation cycle, to prevent neural infiltration of lymphoblasts. However, in cases of Philadelphia chromosome involvement in ALL, imatinib mesylate, a signal transduction inhibitor, should be used throughout the induction, consolidation, and maintenance phases, adding it to the final phase (Brasil, 2014; Hoffbrand & Moss, 2018).

In the consolidation stage of the GBTLI group, a bone marrow analysis is carried out to investigate possible remission. Treatment is twofold: when there is a low response, more intense treatment is followed, using the same antineoplastics as before, with the exception of methotrexate, the dose of which is doubled, as well as the inclusion of two antimetabolites, such as cytarabine and 6-TG thioguanine, cyclophosphamide, an alkylating agent, and the cytotoxic antibiotic vincristine, along with the conjugate of cytarabine and methotrexate, as well as the glucocorticoid dexamethasone - MADIT. Low-risk treatment is followed by cytarabine, cyclophosphamide, 6-mercaptopurine and the MADIT conjugate. After the induction phase, an analysis is carried out and, if there is resistance, the treatment continues with the MADIT conjugate, plus 6-mercaptopurine and methotrexate (Correa et al., 2023; Hoffbrand; Moss, 2018).

In the high-risk treatment, consolidation follows the same protocol, except for the exclusion of cyclophosphamide, as previously mentioned. Still in the consolidation phase, there is a new cycle of infusions, in addition to the MADIT conjugate, cyclophosphamide, isolated 6-mercaptopurine, vincristine and dexamethasone, with the addition of a protein synthesis inhibitor, L-asparaginase and doxorubicin. These increases in the consolidation phase show us a more detailed scheme, with cytotoxicity and inhibition of lymphoblastic cells at different sites of action, longer treatment time and reduced inflammation during the application cycles through the use of the dexamethasone conjugate in MADIT. This differs from the BFM group, which only increases doses and increases antimetabolites and cytotoxic antibiotics, as in the case of methotrexate and etoposide, as well as specific attacks, such as inhibitors of signal transcription, with imatinib mesylate in the case of involvement of the Philadelphia chromosome (Correa et al., 2023; Hoffbrand; Moss, 2018).

Before entering the maintenance phase, both protocols involve an analysis that includes the use of imatinib mesylate, according to the BFM group, along with non-antineoplastic therapies such as radiotherapy and monoclonal antibodies like blinatumomab and inotuzumab, for potential resistance involving B-cell precursors associated with the Philadelphia chromosome. In the GBTLI group, if blast resistance is observed in the bone marrow, a new cycle is initiated with cytarabine, 6-mercaptopurine, methotrexate, and VP16 (etoposide). During the maintenance phase, a combination of methotrexate, 6-mercaptopurine, vincristine, dexamethasone, and MADIT is employed (Correa et al., 2023). This safety measure aims

to track and neutralize any remaining neoplastic cells in cases stratified during previous phases and identified as resistant.

However, after the consolidation phase, another cycle preceding maintenance is carried out, for cases of resistance to the previous cycles, with the addition of ifosfamide, a cytostatic and alkylating agent, along with the drugs already used in the previous phases (Eurofarma, 2021). The standard GBTLI protocol can be modified based on the patient's risk, using combinations of different antineoplastics adapted to each case, such as GBTLI99 for mild cases, GBTLI93 for moderate cases and GBTLI99Ph for severe cases with involvement of the Philadelphia chromosome (Correa et al., 2023). This fact shows the creators' concern for completeness and heterogeneous intensity in the three phases until the end of remission treatment, preserving both remission and the health of the patient, who will often need bone marrow transplants at least twice during treatment.

Among the most commonly used drug classes, cytotoxic antibiotics stand out, followed by antimetabolites, microtubule inhibitors, glucocorticoids, and monoclonal antibodies, primarily presented in different combinations within the GBTLI group's protocol. This approach is due to the expanded therapeutic regimens aimed at targeting malignant cells at various stages of the cell cycle, while continuously monitoring the patient's health status concerning the therapy's effectiveness. In this context, the GBTLI protocol proves to be the most efficient in terms of treatment scope. However, the BFM protocol is notable for its short-term efficacy, achieving rapid remissions of malignant cells with more common and predictable adverse reactions in high-risk patients, compared to the broader GBTLI treatment.

APPLICABILITY RATIO IN LLA

Segundo Lorsch et al. (2023), o protocolo do grupo GBTLI mostrou-se ineficiente no tratamento de alto risco em uma criança de 5 anos com rearranjos do gene KMT2A. Após as fases de indução e intensificação no tratamento da LLA, houve positividade de 1,5% na primeira e 0,5% na segunda para blastos na medula óssea, o que levou à troca do protocolo para St. Jude's R15, com resultados posteriores de 0,01% ainda nas primeiras fases do tratamento. Contudo, não podemos descartar a falta de adição de anticorpos monoclonais ao tratamento, pois estes são direcionados somente para casos de cromossomo Filadélfia. Além disso, é necessária a inativação da proteína anômala codificada pelo gene KMT2A, como foi o caso do Revumenib utilizado no protocolo do grupo St. Jude's R15.

Durante um estudo com a utilização do protocolo BFM 2002, foi possível mensurar os riscos em 100 pacientes com LLA, dos quais 18 (0,05%) foram tratados, sendo que 7 ainda estavam na fase de indução, com cerca de 78 dias, quando, na mesma fase, obteve-se 70% de remissão completa da doença, passando para a fase de consolidação. Contudo, ao final do tratamento, as causas de complicação foram sepse, sangramento, pancreatite na fase 2 de indução e intoxicação por metotrexato devido a bolos de alto risco; ademais, dois pacientes necessitaram de transplante de medula óssea (Khandelwal et al., 2023). Em outro estudo para demonstrar o impacto da utilização da daunorrubicina no tratamento da LLA, segundo o protocolo BFM 2009 no serviço público, verificou-se a extrema necessidade desse medicamento para a eficácia do protocolo, o que influenciou diretamente no tratamento de pacientes crianças e adolescentes, com remissão de células malignas em 98,8% (86) dos 87 pacientes tratados segundo o protocolo (Azevedo et al., 2023).

Porém, altas doses em curta duração não são bem toleradas, o que leva a severidades nos efeitos dos medicamentos no organismo em desenvolvimento, como leucopenia, hemorragias, aplasias medulares, pancreatite e encefalopatias graves. Para mitigar esses efeitos, é necessária a combinação de doses com outros medicamentos, a utilização de anticorpos monoclonais para inativação de proteínas de genes anômalos e a adoção de regimes mais prolongados para a recuperação do organismo da criança. Não se pode descartar deficiências no curso do tratamento, como abandono, não cumprimento adequado do protocolo e falta de tratamento de suporte de alta complexidade. No entanto, tratamentos mais prolongados e com menos intensidade tendem a cursar com faixa subterapêutica, levando à resistência das células malignas ao tratamento e à exaustão do organismo diante do controle de subprodutos tóxicos gerados, bem como ao prolongamento do sofrimento do paciente. Contudo, é necessário um estudo genômico das células malignas envolvidas, das comorbidades, se presentes; é necessário também o tratamento de suporte antes, durante e após esse estudo, analisando os riscos e os benefícios do protocolo empregado. Nesse contexto, apesar do insucesso apresentado no tratamento de adolescentes e crianças de alto risco, o protocolo GBTLI é o esquema mais indicado na atualidade, pois possui um estudo prévio detalhado do paciente, com riquezas de detalhes genômicos e do organismo antes do tratamento.

SECURITY RELATIONSHIP BETWEEN PROTOCOLS

In studies carried out by Prolog et al. (2024) on cytotoxic analysis of lymphoblastic cells, it was observed that during combined induction treatment with chemotherapy, the CD19, CD20 and CD58 markers were destroyed, preventing their tracking and destruction by monoclonal antibodies, making them resistant. The German BFM group's protocol was created with the aim of treating the patient according to the clinic presented in the flow cytometry, separating the groups according to chemotherapy intensity while still in induction, consolidation or, when necessary, maintenance. In another study carried out in a public hospital, an overall survival rate of 83.8% was reported in 116 patients aged between 1 and 18 years who were mapped using the molecular biology method to trace leukemia cells during treatment (Gouveia et al., 2023). In addition, another study of patients aged between 1 and 25 years showed an overall survival rate of 74% in 75 patients treated using the BFM 2009 protocol (Nath et al., 2023).

The regimen refers us to a standard for mild and moderate cases, related to its application according to the patient's risk of refractoriness. However, the high-risk protocol becomes necessary, in which the patient receives up to 6 blocks of chemotherapy in the induction phase and 3 blocks in consolidation in a short time, maintaining a very cumulative regimen with intense consolidation phases. In this protocol, vincristine, daunorubicin, intrathecal L-asparaginase, prednisolone and methotrexate, as well as additional ones such as blinatumomab and rituximab, are used on target cells over short periods.

To reduce the harmful effects of antineoplastics and increase safety during treatment, the GBTLI group opted for dose fractionation and prolonged treatment in its therapeutic protocol, with combined variations of different drugs and monoclonal antibodies in cases involving B-cell precursors. This protocol resulted in a significant reduction in hepatotoxicity, contributing to the decrease in the need for bone marrow transplants from two to just one in cases of drug resistance, which led to a high survival rate among the children (Domingues et al., 2021).

However, serious toxic effects have been observed during treatment, with up to three manifestations occurring in the same patient during the maintenance phase. These effects include liver impairment in 85.9% of cases, febrile neutropenia in 64.4%, and opportunistic infections in 79.4% of the 109 patients treated in the high-risk group. These findings are attributed to prolonged exposure and the potentiated effects of antineoplastics, which, while targeting rapidly developing malignant cells, also harm normal cells in the body. In another study using the GBTLI protocol for ALL, severe allergic reactions were observed, including thrombosis (53%), pancreatitis (20%), anaphylaxis (20%), and diabetes mellitus (20%). Seventy-five percent of these reactions occurred during the induction phase but did not result in death due to the supportive treatment provided for the adverse reactions (Parisdutra et al., 2020).

Thus, the risk associated with the protocols depends on the length of exposure to chemotherapy, with routine transplantation being necessary during both the induction and consolidation stages. The GBTLI protocol, by spacing out treatments, has proven to be the safest during the induction phase due to its better-tolerated effects compared to the BFM protocol. However, adverse reactions from prolonged treatment require extended supportive care. The duration of treatment, in relation to the resistance of malignant cells in ALL, needs reconsideration, especially in cases of high-risk patients with Philadelphia chromosome involvement, which often leads to irreversible alterations in the patient's body. Despite this, the benefits of both protocols outweigh the risks. On the other hand, short-term treatment with high doses of chemotherapy necessitates earlier supportive interventions and may compromise the bone marrow during the induction phase, making treatment more costly and riskier for the patient. Nonetheless, this approach has shown promising results with high cure rates.

Finally, this protocol requires a genomic study to stratify high-risk groups, and these patients should be treated with a protocol that involves more precise detailing of the cells involved and treatment with different classes of antineoplastics, including monoclonal antibodies.

SECURITY IMPACT AND PROTOCOL RISK

When evaluating the safety and risk impact of protocols used in the treatment of ALL, studies following the ALL-BFM protocol showed that L-asparaginase, added early during the induction phase, corroborated an increase in deaths from infections and high hepatotoxicity in high-risk groups for ALL. In addition, of the 405 patients on randomized treatment with additional L-asparaginase at the start of induction and consolidation, 12 had these adverse effects, out of a total of 809 patients. This was not satisfactory with L-asparaginase when compared to the positive evolution of the control treatment with 404 low-risk patients (Conter et al., 2022). These findings indicate that intensive treatment with L-asparaginase was not effective for high-risk patients, but contributed positively to patients with additional treatment. Despite the benefits of treatment for low-risk patients, the intensified protocol proved ineffective and had a negative effect on the improvement of high-risk patients when L-asparaginase was administered in high doses. This required, in addition to supportive treatment, bone marrow transplantation and special care, as well as vigilance during the administration of the drugs in each phase.

On the other hand, studies using the GBTLI protocol in the Unified Health System (SUS) showed that, over three years of treating patients with pediatric ALL, the mortality rate was 12.8% (303) out of a total of 15,186 patients. This highlights that, although the Public Health Service makes efforts with the purchase of first-line drugs, drug standardiza-

International Journal of Biological and Natural Sciences ISSN 2764-1813 DOI https://doi.org/10.22533/at.ed.813522527027

tion, and child health programs, late diagnosis and system overload have contributed to the resistance of malignant cells and worsening of treatments (Seber et al., 2021). Additionally, another study using the GBTLI protocol to assess central nervous system involvement with the use of triple doses of methotrexate in children undergoing chemotherapy resulted in 9.5% (16/160) of patients experiencing some neurological complication. These complications included brain damage in 35.9%, seizures in 25%, stroke in 18.75%, headache in 18.75%, learning deficits in 18.75%, hearing loss in 12.5%, leukoencephalopathy in 6.25%, dissociative disorder in 6.25%, and migraine in 6.25%, with 37.5% of these complications occurring during the induction phase, 37.5% after the consolidation phase, and 6.25% during the maintenance phase (Silva et al., 2020).

However, these findings are frequent, especially due to the high doses of MTX during the prevention of central nervous system infiltration, requiring supportive treatment or, in other cases, changing the chemotherapy drug for another with the same clinical indication and multidisciplinary monitoring to improve the choice of the best dosage regimens. Although adverse effects have been reported, this protocol has been the safest due to its initial treatment planning, with mapping of the genome involved in the malignant cells. Prolongation with more widely spaced doses, the use of different chemotherapies, as well as combined treatment at different sites and phases of the cell cycle, also contribute to this safety.

Finally, treatment using the BFM group's protocol follows a scheme with a massive attack on neoplastic cells, with high doses of chemotherapy still in the induction phase, maintaining a simple treatment scheme with four drugs, moving on to the consolidation phase and an increase in the maintenance phase with a reduction in intensity. However, this type of regimen has been reported with the association of monoclonal antibodies, facilitating traceability and treatment efficacy. However, more careful planning is needed so as not to mask the results, avoiding suppression of the expression of specific surface antigens manifested in neoplastic cells

CONCLUSION

In summary, antineoplastic chemotherapy interactions, when manifested in the BFM and GBTLI protocols, are in many cases the result of multicenter therapeutic planning in the antineoplastic response to ALL, which outweighs the undesirable and tolerable effects of the treatment. Significant interactions include the synergism between daunorubicin, vincristine, prednisolone or dexamethasone together with L-asparaginase, which has been found to result in remission of up to 70% to 90% for the BFM and GBTLI protocols. However, in cases of massive or prolonged exposure, it corroborated serious effects such as hepatotoxicity and severe bone marrow depression, requiring up to two transplants, as presented by the BFM. In the GBTLI, other effects occurred, such as cardiotoxicity, severe bone marrow depression, pancreatitis and anaphylactic shock, but only required one bone marrow transplant in severe cases with prolonged treatment.

In addition, the historical series of the development of the BFM 2009 and GBTLI 2019 protocols has shown that therapeutic regimens are becoming increasingly strategic to shape the response of antineoplastic drugs to the profile presented at diagnosis. The GBTLI group's protocol, for example, shows better results compared to the BFM. This can be seen in the extra- and intracellular responses, with the stratification of normal and diseased cells. This distinction is made by tracing antigens expressed on the surfaces of remaining lymphoblasts, using monoclonal antibodies during the final stages of treatment.

However, this does not detract from the results achieved by the BFM protocol in the past. The standardization of the classes of antineoplastics used for the treatment of ALL, together with the effort to make the GBTLI protocols applicable by the Brazilian public and private health system, has moved the multidisciplinary team in specific child treatment centers and demonstrated good results in recent years in the treatment of childhood ALL between the ages of 1 and 4. However, it is still a challenge in severe cases of the disease in adolescents and young adults.

In short, this situation highlights the need to address and plan more studies for the improvement and development of existing protocols. It is essential that genetic mapping is implemented in all treatment centers, as well as research into the benefits of treatment with monoclonal antibodies. In addition, it is crucial to consider its use in tracking and monitoring neoplastic cells during treatment, promoting a cure and prolonging and maintaining life with greater comfort and dignity for the ALL patient.

REFERENCES

AGÊNCIA EUROPEIA DE MEDICAMENTOS. Oncaspar 750 U/ml solução injetável ou para perfusão.Viena: Baxalta Innovations GmbH, 2016

Aspen Pharma Indústria Farmacêutica Ltda. **PURINETHOL® mercaptopurina.** Serra-ES. Divisão de estudos clínicos, 2021.

Aspen Pharma Industria Farmaceutica. **Lanvis® Tioguanina.** Serra: Lavis Bu Pac, 2017**.**

AZEVEDO, AC. et al. Impacto do uso de idarrubicina na terapia de indução da leucemia linfoide aguda de acordo com o protocolo AIEOP-BFM ALL 2009. Experiência do Centro Infantil Boldrini. Hematol Transfus Cell Ther. São Paulo, v. 45, n.04, p.581, october. 2023.

BARBOSA, TC. et al. Unexpected concomitance of ETC6-RUNX1 and BCR-ABL1P210 in a child with B-CELL precursor acute lymphoblastic leucemia. Hematol Transfus Cell Ther. São Paulo, v.43, n.01, p.304, outubro. 2021

Baxter Oncology GmbH. **Genuxal ciclofosfamida monoidratada.** Halle/Westfalen, Alemanha: Divisão de estudos clínicos, 2021.

BELTRAME, MP. et al. Leucemia aguda indiferenciada. Hematol Transfus Cell Ther. São Paulo, v.45, n.04, p.588, october. 2023.

Blau Farmacêutica S.A. **CITARAX® citarabina.** Cotia:2016.

Blau Farmacêutica S.A. **EPÓSIDO® etoposídeo.** Cotia: Divisão de estudos clínicos, 2019.

Blau Farmacêutica S.A. **METREXATO® metotrexato de sódio.** Cotia: Divisão de estudos clínicos, 2023.

BOAVIDA, Helena Matilde Dias. **Leucemia Linfoblástica Aguda: uso de protocolos pediátricos em adolescentes e adultos jovens.** Lisboa, 2021, p.19-22, Dissertação (Mestrado Integrado em Medicina). Faculdade de Medicina Lisboa, Universidade de Lisboa.

Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. **Protocolos clínicos e diretrizes terapêuticas em Oncologia**. Brasília: MS, 2014.

CEPPI, Francesco et al. Near-tetraploid T-cell acute lymphoblastic leukaemia in childhood: Results of the AIEOP-BFM ALL studies. **European Journal of Cancer** . Europa. Ago. 2022. CADERNO 175, p. 120-124.

Conselho de Ética médica. **Conselho de Ética Médica aprova novo protocolo de tratamento contra LLA.** ABRALE/Notícias, 2022. Disponível em:https://abrale.org.br/noticias/conselho-de-etica-medica-aprova-novo-protocolo-de-tratamento-contra-lla/Abrale.org.htm. Acesso em:08 de abril de 2024. Abrale.org.htm. Acesso em:08 de abril de 2024.

CONTER, Valentino et al. Impacto da terapia intensiva adicional com L-asparaginase durante a fase de consolidação para leucemia linfoblástica aguda de alto risco: resultados de um ensaio clínico randomizado no protocolo AIEOP-BFM ALL 2009. Publicações ASH. Washington v.140, n.01, p.109-111, nov. 2022.

CORREA, Bruno Terra et al. Association of the clinical profile and overall survival of pediatric patients with acute lymphoblastic. Frontiers in Pediatrics. Spain, v.01, n.01, Set. 2023.

DOMINGUES, LDS. et al. A associação de Blinatumomab (BLINA) e Inotuzumab (INO) pode inuzir resposta completa de leucemia linfoide aguda de linhagem B (LLA-B) refratária e permitir o transplante de células-tronco hematopoiéticas (TCTH) em remissão. Hematol Transfus Cell Ther. Hematol Transfus Cell Ther. São Paulo, v.43, n.01, p.147-148, outubro. 2021.

Eurofarma Laboratórios S.A. **ifosfamida**. Itapevi: 2021.

GOUVEIA, AB. et al. Risk stratification in children with acute lymphoblastic leucemia in therapy according to BFM 2009 adapted protocol. Hematol Transfus Cell Ther. São Paulo, v.45, n.04, p.574-575, october. 2023.

HOFFBRAND, A. Victor; MOSS, Paul A. H. **Leucemia Linfoblástica Aguda. Fundamentos da Hematologia de Hoffbrand.** 7 ed. Porto Alegre: Mercado Aberto, 2018.

KHANDELWAL, Vipin et al. Treatment of newly diagnosed paediatric acute lymphoblastic

LAGUA, Ana et al. **Perfil imunológico aprofundado em crianças com BCP-ALL no estudo AIEOP-BFM ALL 2017.** Publicações ASH. Washington, v.142, n.01, p.595, Nov. 2023.

Libbs Farmacêutica Ltda**. FAULDVINCRI (sulfato de vincristina).** São Paulo: FAULDV, 2014.

LOSCH, BK et al. Leucemia Linfoide Aguda de alto risco com doença residual mensurável persistentemente positiva. Caxias do Sul, v.45, n.4, p.289-290, Out. 2023.

MATOS RM, et al**.** NGS Studiens Reveal Genomic Variant Sin 6Pediatric Patients Diagnosed Witha Cute Leukemia Presenting Rare Cytogenetic Abnormalities. **Hematol Transfus Cell Ther**.São Paulo, v. 4, n. 45, p.586-587, Out. 2023.

Merck Sharp & Dohme Farmacêutica Ltda. **METICORTEN® prednisona**. Campinas, São Paulo: Divisão de estudos Clínicos, 2021.

MORIN, Maria Garcia, et al. Monitoring asparaginase activity toimprove the management of patientswith acute lymphoblastic leukemia: Experience in one center**. Anales de Pediatría.** Badajoz: v.100 n.1, p.65-66 January. 2024.

NATH, Uttam Kumar et al. Measurable Residual Disease Results & Survival with Augmented Early Intensification Therapy in Intermediate-Risk & High-Risk Group Pediatric Acute Lymphoblastic Leukemia Patients Treated with ALL IC-BFM 2009 Protocol: A Single-Center Study from India. Blood TVH vessels, Thrombosis & hemostasis. ASH PUBLICATIONS, 2023.

OLIVEIRA, LP. et al. Tratamento de resgate com inibidor do BCL-2 (VENETOCLAX) em paciente com recidiva da Leucemia linfocítica Agudalinfocítica aguda (LLA) pós transplante de medula óssea (TMO). Hematol Transfus Cell Ther.São Paulo, v.44, n.02, p.333, october.2022.

PARISDUTRA, M. et al. Avaliação de complicações associadas ao tratamento com asparaginase nos pacientes com LLA. **Hematol Transfus Cell Ther.** São Paulo, v.42, n.02, p.303, novembro. 2020.

PONTES RM. et al. Reliable Flow Cytometri Method for monitoring Ofminimal Redisual Disease in Patients With B-Cell Precursora Acute Lymphoblastic Leukemia After Blinatumomab Therapy. **Hematol Transfus Cell Ther**. v. 4, n. 45, p.587-588 Out. 2023.

PRELOG, Tomaz et al. **The influence of cytotoxic drugs on the immunophenotype of blast cells in paediatric B precursor acute lymphoblastic leukaemia.** Sciendo.Radiol Oncol.Slovenia, v.58, n.01, p.133-144, Jan. 2024.

SEBER, Adriana et al. Leucemia Linfoblástica Aguda Pediátrica: Análise de Banco de Dados de Pacientes e Tratamentos em um Sistema Nacional de Saúde Pública. Publicações ASH. Washington v.138, n.01, p.905, Nov. 2021.

SILVA, B. et al. Avaliação de complicações em sistema nervoso central durante o tratamento quimioterápico pelo protocolo GBTLI 2009 em uma única instituição**. Hematol Transfus Cell Ther.** São Paulo, v.42, n.01, p.304, novembro. 2020.

WEBER, Fernanda et al.Treatment of acute lymphoid leukemia in children: a narrative review. **Brazilian Journal of Development.** Curitiba, 12 de Abr. 2023.v.09, n.04, p. 13353-13369.

Wyeth Indústria Farmacêutica Ltda. **DAUNOBLASTINA® (cloridrato de daunorrubicina).** New Dalhi. 19 de Maio. 2023. CADERNO 8, p.218-223. São Paulo: LL-PLD-Daupoi, 2018.

leukaemia on BFM-based chemotherapy protocol: Feasibility and outcome from a tertiary care center in India. **Pediatric Hematology Oncology Journal.** New Dalhi. 19 de Maio. 2023. CADERNO 8, p.218-223.

MATOS RM, et al**.** NGS Studiens Reveal Genomic Variant Sin 6Pediatric Patients Diagnosed Witha Cute Leukemia Presenting Rare Cytogenetic Abnormalities. **Hematol Transfus Cell Ther**.São Paulo, v. 4, n. 45, p.586-587, Out. 2023.

PONTES RM. et al. Reliable Flow Cytometri Method for monitoring Ofminimal Redisual Disease in Patients With B-Cell Precursora Acute Lymphoblastic Leukemia After Blinatumomab Therapy. **Hematol Transfus Cell Ther**. v. 4, n. 45, p.587-588 Out. 2023.

SILVA, B. et al. Avaliação de complicações em sistema nervoso central durante o tratamento quimioterápico pelo protocolo GBTLI 2009 em uma única instituição**. Hematol Transfus Cell Ther.** São Paulo, v.42, n.01, p.304, novembro. 2020.

OLIVEIRA, LP. et al. Tratamento de resgate com inibidor do BCL-2 (VENETOCLAX) em paciente com recidiva da Leucemia. São Paulo, v.45, n.04, p.574-575, october. 2023. 13353-13369.

Disponívelem:https://ashpublications.org/blood/article/142/Supplement%201/2880/500329/Vinpocetine-Mediates-Therapeutic-Activity-Alone São Paulo: LL-PLD-Daupoi, 2018.

BOABIDA, Helena Matilde Dias. **Leucemia Linfoblástica Aguda: uso de protocolos pediátricos em adolescentes e adultos jovens.** Lisboa, 2021, p.19-22, Dissertação (Mestrado Integrado em Medicina). Faculdade de Medicina Lisboa, Universidade de Lisboa. Disponível em:https://abrale.org.br/noticias/conselho-de-etica-medica-aprova-novo-protocolo-de-tratamento-contra-lla/

Merck Sharp & Dohme Farmacêutica Ltda. **METICORTEN® prednisona**. Campinas, São Paulo: Divisão de estudos Clínicos, 2021.

HOFFBRAND, A. Victor; MOSS, Paul A. H. Leucemia Linfoblástica Aguda. Fundamentos da Hematologia de Hoffbrand. 7 ed. Porto Alegre: LAGUA, Ana et al. **Perfil imunológico aprofundado em crianças com BCP-ALL no estudo AIEOP-BFM ALL 2017.** Publicações ASH. Washington,