Journal Pre-proof

COVID19 and acute lymphoblastic leukemias of children and adolescents: first recommendations of the Leukemia committee of the French Society for the fight against Cancers and Leukemias in children and adolescents (SFCE)

André Baruchel Yves Bertrand Nicolas Boissel Benoit Brethon Stéphane Ducassou Virginie Gandemer Carine Halfon-Domenech Thierry Leblanc Guy Leverger Gérard Michel Arnaud Petit Anne-France Ray-Lunven Pierre-Simon Rohrlich Pascale Schneider Nicolas Sirvent Marion Strullu, for the SFCE Leukemia Committee

PII: S0007-4551(20)30201-0

DOI: https://doi.org/doi:10.1016/j.bulcan.2020.04.003

Reference: BULCAN 915

To appear in: *Bulletin du Cancer*

Received Date: 21 April 2020

Accepted Date: 24 April 2020

Please cite this article as: A. Baruchel, Y. Bertrand, N. Boissel, B. Brethon, S. Ducassou, V. Gandemer, C. Halfon-Domenech, T. Leblanc, G. Leverger, G. Michel, A. Petit, A.-F. Ray-Lunven, P.-S. Rohrlich, P. Schneider, N. Sirvent, M. Strullu, for the SFCE Leukemia Committee, COVID19 and acute lymphoblastic leukemias of children and adolescents: first recommendations of the Leukemia committee of the French Society for the fight against Cancers and Leukemias in children and adolescents (SFCE), *Bulletin du Cancer* (2020), doi: https://doi.org/10.1016/j.bulcan.2020.04.003

COVID19 and acute lymphoblastic leukemias of children and adolescents: first recommendations of the Leukemia committee of the French Society for the fight against Cancers and Leukemias in children and adolescents (SFCE)

COVID19 et leucémies lymphoblastiques aiguës des enfants et des adolescents : premières recommandations du « comité leucémie » de la Société Française de lutte contre les Cancers et les Leucémies chez les enfants et les adolescents (SFCE)

André Baruchel[1]*, Yves Bertrand[2], Nicolas Boissel[3], Benoit Brethon[1], Stéphane Ducassou[4], Virginie Gandemer[5], Carine Halfon-Domenech[2], Thierry Leblanc[1], Guy Leverger[6], Gérard Michel[7], Arnaud Petit[6], Anne-France Ray-Lunven[1], Pierre-Simon Rohrlich[8], Pascale Schneider[9], Nicolas Sirvent[10], Marion Strullu[1], for the SFCE Leukemia Committee

[1] Service d'Hémato-Immunologie Pédiatrique Hôpital Universitaire Robert Debré APHP et Université de Paris

[2]Institut d'Hémato-Oncologie Pédiatrique, CHU Lyon, Lyon

[3]Unité Adolescents et Jeunes Adultes, Hôpital Saint-Louis, APHP et Université de Paris

[4]Unité d'Hémato-Oncologie Pédiatrique, Groupe Hospitalier Pellegrin, Bordeaux

[5] Service d'Hémato-Oncologie Pédiatrique, CHU Rennes

[6] Service d'Hémato-Oncologie Pédiatrique Hôpital Armand-Trousseau APHP et Sorbonne Université

[7] Service d'Hématologie Pédiatrique, CHU la Timone, Marseille

[8]Service d'Hémato-Oncologie Pédiatrique, CHU l'Archet, Nice

[9] Service d'Hématologie Pédiatrique, CHU Charles Nicolle, Rouen

[10] Service d'Hématologie et Oncologie Pédiatrique, CHU Arnaud de Villeneuve, Montpellier

* **Auteur correspondant** : André Baruchel
Service d'Hémato-Immunologie Pédiatrique Hôpital Universitaire Robert Debré APHP et Université de Paris
e-mail : andre.baruchel@aphp.fr

Summary

Since the emergence of the SARS-CoV-2infection, many recommendations have been made. However, the very nature of acute lymphoblastic leukemias and their treatment in children and adolescents led the Leukemia Committee of the French Society for the fight against Cancers and leukemias in children and adolescents (SFCE) to propose more specific recommendations, even if data for this population are still scarce. They may have to evolve according to the rapid evolution of knowledge on COVID19.

Keywords: SARS-CoV-2- COVID 19- Acute lymphoblastic leukemia-children-adolescents

Résumé

Depuis l'émergence de l'infection à SARS-CoV-2, de nombreuses recommandations ont été émises. Cependant la nature de la maladie et du traitement des leucémies aiguës lymphoblastiques de l'enfant et de l'adolescent a conduit le Comité Leucémies de la Société Française de lutte contre les Cancers et Leucémies de l'enfant et de l'adolescent (SFCE) à proposer des recommandations plus spécifiques, même si les données concernant cette population sont encore très parcellaires. Elles pourront être amenées à évoluer en fonction de l'évolution rapide des connaissances sur l'infection COVID19.

Mots clés : SARS-CoV-2- COVID19- Leucémie aiguë lymphoblastique-enfants-adolescents

Preamble and general recommendations:

Few cases of acute lymphoblastic leukemia (ALL) with COVID-19 infection have been reported so far during the pandemic, and the course has been generally mild (1-3). Thus, the main threat to children with ALL, especially those in remission, remains the ALL itself, even if rare serious and life-threatening infections are emerging (4).

There are currently insufficient data to support recommendations applicable to all local cases and situations during the care of children and AYA with ALL. The most experienced practitioners of the hematology-oncology unit must therefore help to

decide, on a case-by-case basis, for which patients should the leukemia treatment be initiated or continued, or identify those in whom a delay is possible, depending clinical and tumor biology. For patients in the advanced stage of their disease, the real benefit of the treatment in the context of the risk of COVID-19 must be considered and discussed.

It is recommended to test for SARS-CoV-2 before starting intensive chemotherapy or an intensive phase of treatment, for ALL patients, with or without symptoms. If patients are tested positive for SARS-CoV-2, one should delay systemic treatment if possible (e.g. absence of major hyperleukocytosis). If the SARS-CoV-2 test is not available, carefully look for suggestive symptoms (dry cough, high fever, anosmia, digestive signs) and consider a chest CT scan. As soon as available, serological tests should be implemented in all patients.

It is necessary to insist on the need, in particular in the regions with high prevalence, to "over-isolate" a child or adolescent COVID-negative to allow him to securely advance in the treatment (facial mask, barrier measures, no contact with suspect COVID or COVID + for 3 weeks ...), in particular those intended to be allografted.

Patients with ALL in first line, included in the CAALL-F01 protocol or treated according to the FRALLE / EORTC protocols, ESPhALL 2017, INTERFANT 06

Are you changing your approach to initial induction?

General considerations

There is a controversy about the use of steroids, a key part of induction therapy.

We consider that the risk-benefit ratio calls for regular protocol induction.

If the physician considers that the patient is at high risk of complications, we recommend a multidisciplinary discussion and / or with the coordinators of the protocol with a view to considering reductions in dose or in the number of administrations of certain drugs including potentially steroids. Once all the induction chemotherapy has been administered, the use of G-CSF in a COVID + patient can be discussed to reduce the duration of neutropenia.

The implementation of all or part of treatment on an outpatient basis must be carefully weighed. Indeed, the comings and goings to the ambulatory clinic and blood samplings at home increase the number of contacts at risk. Conversely, return at home could limit contact with caregivers, also possibly contaminated.

In most hospitals, visits are limited to only parents, with only one parent present at a time.

Note that the risk of needing an intensive care bed during induction therapy is low (probably <5%). However, in certain regions, the decrease in the number of pediatric ICU beds (transformed into adult resuscitation beds) implies that the pediatric need is being forcefully re-expressed.

Specific populations

a. Philadelphia chromosome ALL: some adult hematologists (see ASH adult ALL COVID19 recommendation) offer treatment with a tyrosine kinase inhibitor with minimal steroid exposure rather than aggressive induction with multidrug therapy for the initial treatment, in the hope of avoiding prolonged hospitalization during the pandemic. However, the recommendation to include our patients in the EsPhall 2017 protocol seems appropriate to us.

b. Infants under one year of age: the risk of serious forms of COVID19 in infants has been reported. The test for SARS-CoV-2, possibly repeated, is absolutely necessary here. Again, the recommendation is to follow the current guidelines i.e. to follow the Interfant 06 protocol.

c. Adolescents and young adults: take into account the risk factors observed in adults, asthma, obesity, diabetes. Insist on compliance with treatment in general but also on that linked to containment measures and barrier gestures.

d. Children with Down syndrome: vigilance is essential in these children susceptible to infections in general, even if this susceptibility rarely concerns viral infections. Of note this group benefits from an induction with "only" 3 drugs in the CAALL-F01 protocol.

Are you changing the approach to intensive post-remission therapy (consolidation, delayed intensification)?

In the absence of data, our recommendation is to follow the protocol, including for corticosteroid therapy.

For patients with high-risk ALL, an individualized decision regarding transplantation and its timing is necessary, weighing the risks of transplantation in an epidemic context of COVID-19 against the risk linked to ALL.

Are you changing your recommendations for maintenance treatment?

Three problems are mainly to be discussed :

- Intensity of maintenance treatment with 6MP / MTX and targets for leukocytosis / neutrophils / lymphocytes: we suggest to follow the usual recommendations of the protocol.

- pulses : monthly pulses (CAALL-F01, B-SR group) or every 10 weeks (CAALL-F01, B-MR group) with vincristine and steroids are to be maintained. COVID19 testing the day before could be useful if feasible: if COVID +, then postpone the pulse for about 2 weeks.

- High dose methotrexate cycles in maintenance for T-ALL with high initial leucocyte count (≥ 100 G/L) and/or CNS3 status : any concern could be discussed with the protocol coordinators.

In addition, minimizing hospital visits seems appropriate. Monitor patients as much as possible via telemedicine and home blood tests.

Patients with second line or more ALL:

- First relapse: we propose to include all eligible patients and to follow the INTREALL protocol as much as possible. Patients who reach complete remission n°2 should be considered promptly for allogeneic transplantation, as indicated in the protocol, despite the pandemic.

- Second relapse and refractory relapses :

  • Phase I-II trials: it is likely that almost all academic or industrial promoters will ask for SARS-Co-V2 testing before inclusion and that any positivity will be an exclusion criterion, at least temporarily.

  • CAR-T cells: The indication for treatment with CAR-T cells must be weighed with the center which would perform them: feasibility of performing apheresis (systematic patient testing, problem of using an operating room for the special catheter placement for example)? Manufacturing feasibility? Feasibility of administration according to the possible places in intensive care unit ?

What to do if an ALL patient is diagnosed with SARS-CoV-2 infection? What are the interactions between ALL chemotherapy and potential COVID-19 therapy?

General recommendations

1. The diagnosis of SARS-CoV-2 infection during the treatment of ALL should imply to discuss the stopping and / or postponing of all chemotherapies, according to the severity of the ALL, the stage of treatment and the severity of clinical and / or radiological signs. Even if severe forms have been recently described, most of the experience is currently reassuring (2-4)

2. Any "specific" treatment must be discussed with the infectious disease team.

Potential interactions

They are described in Table 1 aiming to list some of the treatments with antiviral potential and some of those proposed to act against the inflammatory process. Of

note, the inflammatory stage of covid19 infection is generally the one of aggravation, and often involves hospitalization in ICU. Chemotherapy is obviously interrupted at this stage.

Conclusion

These recommendations have to be updated in the future with more experience and more data gathered at the national and international level and in the evolving context of the pandemic and the weapons to combat it.

(Version 1.0; last update 20.04. 2020)

Conflicts of interest : no conflict to declare for all authors

Références

1. SARS-CoV-2 Infection in Children. Link https://www.ncbi.nlm.nih.gov/pubmed/32187458

2. Hrusak O, Kalina T, Wolf J, Balduzzi A, Provenzi M, Rizzari C et al. Flash Survey on SARS-CoV-2 Infections in Pediatric Patients on anti-Cancer Treatment. Eur J Cancer. 2020 Apr 7 - doi: 10.1016/j.ejca.2020.03.021

3. Balduzzi A, Brivio E, Rovelli A, Rizzari C, Gasperini S, Melzi ML et al. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Bone Marrow Transplantation (In press).

4. André N, Rouger-Gaudichon J, Brethon B, Phulpin A, Thebault E, Pertuisel S et al for the Société Française de lutte contre les Cancers et leucémies de l'Enfant et de l'adolescent (SFCE). COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: high-risk of severe forms? Pediatr Blood Cancer 2020 (in press)

Table 1

Treatments with antiviral potential :

- Hydroxychloroquine (OHQ): unproven efficacy
    - o does not interact with methotrexate or 6-MP
    - o be cautious about the use of OHQ with other agents prolonging the QTc interval such as azoles, macrolides, levofloxacin, Tyrosine Kinase Inhibitors ++.
- Remdesivir: unproven efficacy
    - o can be obtained in compassionate use in children (Gilead).
    - o described elevation of transaminases. No clear concept on drug interactions (check and update if co-prescription)
- combination of lopinavir / ritonavir: unproven efficacy
    - o may increase the concentration of methotrexate, monitoring is therefore suggested without empirical dose adjustment.
    - o there is an interaction with vincristine. Dose reduction to be considered.
    - o no interaction with 6 MP, daunorubicin or pegaspargase.

Treatments acting on the consequences of inflammation

- tocilizumab: unproven efficacy
    - o no obvious interactions with chemotherapy.
- anakinra: unproven efficacy
    - o no obvious interactions with chemotherapy
- eculizumab: unproven efficacy
    - o protocol in progress in adults
- corticosteroids: controversial use in the setting of SARSCov2 infection.