ALL-IC REL 2022 guidance

concise summary

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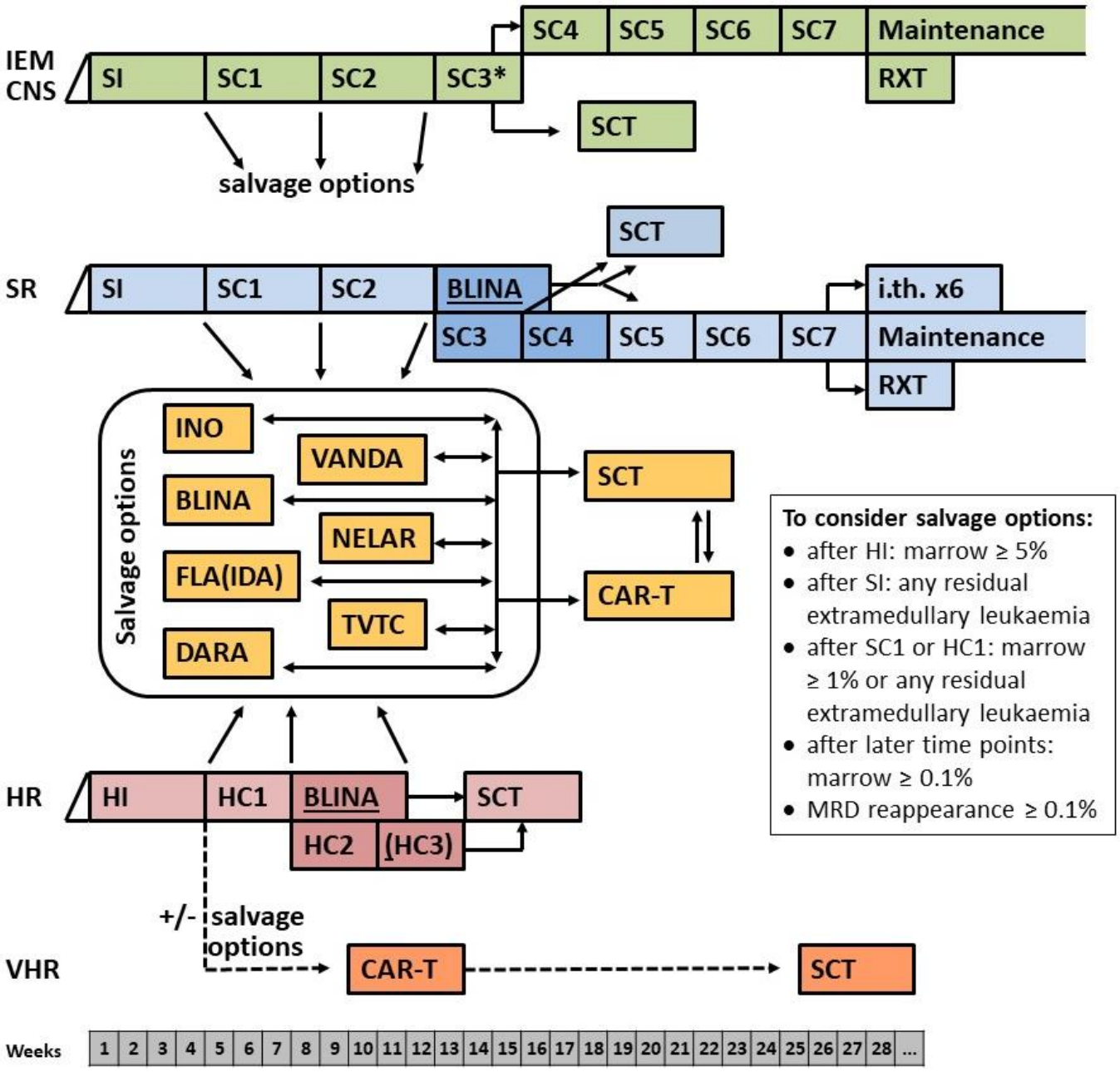
Overview:



Introduction

Regarding the optimal treatment of 1st relapses of paediatric acute lymphoblastic leukaemia, large amount of new knowledge has been gained since the release of the latest 1.1 version of the ALL-IC REL guidance (dated September 2019). Here, we summarize the recommended changes from that protocol and the outline of the new guidance.

The recommendations in this document are a current best practice guidance optimized for ALL-IC countries. The aim was to establish a framework that

- allows and guides the use of most recent, most expensive novel therapies;
- provides guidance for centres where novel therapies are not available or not possible to get funded;
- allows for cooperation with the IntReALL studies as much as possible.

The guidance is a recommendation only without any legal binding to any centres applying it or local modifations to it. This short summary gives centres a chance to apply new knowledge immediately after its edition. It is estimated to take longer time to write the detailed full protocol which will follow.

1. Definitions and risk stratification

The choice of treatment backbone (see figure on front page) is based on risk group stratification. Risk group stratification of relapses will change to follow that of the IntReALL BCP 2020 guidance. Instead of two previous risk groups, now four groups are separated:

	Non-T-cell				T-cell	
	Non-high risk genetics		High risk genetics			
	Isol. extra-med. CNS	Others	Isol. extra-med. CNS	Others	Isol. extra-med. CNS	Others
Very early	IEMC	VHR	IEMC	VHR	IEMC	VHR
Early	IEMC	HR	IEMC	VHR	IEMC	HR
Late	IEMC	SR	IEMC	VHR	IEMC	HR

Abbreviations: CNS, central nervous system; Extramed., extramedullary; HR, high risk; ; IEMC, isolated extramedullary relapses with CNS involvement; Isol., isolated; SR, standard risk; VHR, very high risk.

To define the categories regarding time to relapse are unchanged:

Time-point	After primary diagnosis		After completion of primary therapy
Very early	< 18 months	and	< 6 months
Early	≥ 18 months	and	< 6 months
Late			≥ 6 months

To define the categories regarding location of relapse:

Bone marrow		**< 5% blasts**	**≥ 5% blasts**
Extramedullary relapse	No	See text below	Isolated bone marrow relapse
	Yes	Isolated extramedullary relapse	Combined bone marrow / extramedullary relapse

Regarding defining relapse, remission and treatment failure, the ALL-IC REL group adheres to the new 2021 Ponte-di-Legno consensus (Buchman et al, Blood; 139(12):1785-). According to this, even 1% of bone marrow blasts are enough to define relapse, though only if conformed by more testing methods and/or times of testing.

High risk genetic features:

- *TP53* alterations
- *KMT2A-AFF1* fusion – t(4;11)(q21;q23)
- *TCF3-PBX1* fusion – t(1;19)(q23;p13)
- *TCF3-HLF* fusion – t(17;19)(q22;p13)
- low hypodiploidy

Philadelphia positive relapses and those with ABL-class fusions are suggested to be treated as the above features (immunophenotype, location and time of relapse) stratify their treatment guidance but with the addition of tyrosine kinase inhibitors to chemotherapy. At baseline this should be imatinib, but if available, then we recommend dasatinib for patients with CNS involvement and for those who relapsed after imatinib used in frontline therapy.

Allogeneic haematopoietic stem cell transplantation (SCT) is indicated in all T-cell relapses. Regarding non-T immunophenotype relapses, SCT indications are highlighted in the table below - following that of the IntReALL BCP 2020 group:

	SR			HR/VHR	IEMC	
	MRD GR	MRD PR	MRD ND		Late	Early
MD*	No	Yes	Yes	Yes	No	Yes
MMD**	No	Yes	Yes	Yes	No	Yes

* Matched donor is defined as at least 9 out of 10 HLA alleles identical with high-resolution typing of HLA A, B, C, and DQ, DR. ** Mismatched donor is defined as less than 9 out of 10 HLA alleles identical (= more than 1 antigen mismatch).
Abbreviations: GR, good response as defined by end induction MRD < 0.1% in the SR group; MD, matched donor; MMD, mismatched donor; MRD, minimal residual disease after induction; ND, not done; PR, poor response as defined by end induction MRD ≥ 0.1% in the SR group.

2. Isolated extramedullary relapses with central nervous system involvement (IEMC): to be treated with REZ-BFM backbone

Background: Based on unpublished data from the IntReALL group, these patients do better on the classic ALL BFM REZ backbone than on the R3 backbone. Among previous SR patients, this was the only one group whose survival didn't improve on blinatumomab arms as per oral publications from the COG study.

To define isolated extramedullary relapses with central nervous system involvement, all three of the below requirements are met:

- overt CNS relapse: (a) CSF WBC >5/µl and/or (b) focal neurological signs and/or (c) CNS mass detected on MR or CT scan
- lymphoblasts can be identified in CSF or in biopsy
- bone marrow involvement <5%

Recommendation: Irrespective of immunophenotype and time to relapse, these patients are to be treated with the same chemotherapy backbone. This is the same therapy as the SR arm treatment of the ALL-IC REL 2016 protocol version 1.1. However, their HSCT indication will differ. Those with early and very early relapses, or those with T-immunophenotype, or those with HR genetics, or those with non-remission at the end of induction are advised to be subjected to SCT after the 4th cycle.

The IntReALL group plans to replace the SC3 block with a cycle of blinatumomab in the IEMC arm. It is not a violation of the ALL-IC REL 2022 guidance to follow that practice.

3. SR arm, blinatumomab instead of two consolidation cycles

Background: A COG study has recently proven the benefit of blinatumomab when replacing chemotherapy in a cohort of low risk 1st relapse in a randomised trial. See:
https://ash.confex.com/ash/2021/webprogram/Paper147946.html
https://lymphoblastic-hub.com/medical-information/aall1331-blinatumomab-improves-outcomes-for-some-low-risk-pediatric-and-aya-patients-with-first-relapse-of-b-all

Recommendation: By default, blinatumomab should be given and two SC cycles (SC3 and SC4 type, one each) omitted instead from the ALL-IC REL 2016 protocol version 1.1 (Sept. 2019).

It is an option to adhere to the ALL-IC REL 2016 protocol version 1.1 (Sept. 2019) without giving blinatumomab but giving all SC cycles in the following situations:

- any contraindication of blinatumomab, e.g. CSF WBC > 5/ul or CNS infiltration seen radiologically at the time when blinatumomab would be administered;
- in case of severe blinatumomab toxicity;
- CD19neg cases;
- if blinatumomab is not available.

4. HR arm, blinatumomab instead of HC2 and HC3

Background: Two published phase-3 studies demonstrated the great benefit of blinatumomab over consolidation chemotherapy in high risk 1st relapses. See Locatelli et al. JAMA 2021 Mar 2;325(9):843-854. and Brown et al. JAMA 2021 Mar 2;325(9):833-842. The IntReALL 2020 strategy will randomize inotuzumab with HI, give only one consolidation cycle (HC1) followed by one cycle of blinatumomab, then transplant.

Recommendation: By default, blinatumomab is preferred over HC2 and HC3 in the ALL-IC REL 2016 protocol version 1.1. Exceptions, when HC2 and HC3 should be chosen instead of blinatumomab:

- for T-ALL or any other CD19neg cases;
- in case of severe blinatumomab toxicity;
- any contraindication of blinatumomab, e.g. CSF WBC > 5/ul or CNS infiltration seen radiologically at the time when blinatumomab would be administered;
- if blinatumomab is not available.

5. Defining the very high risk (VHR) group

Background: We were informed about unpublished data from the IntReALL group regarding identified poorest prognostic subgroups. Less than 30% long term survival is achievable with conventional chemotherapy and SCT among these 1st relapse cohorts:

- very early relapses;
- those with high risk genetic features as listed on page 3.

Recommendation: If available, a preferred option may be CAR-T treatment with or without subsequent SCT in precursor-B immunophenotype cases. Participation in phase 1-2 trials, use of available immunotherapies and targeted biological therapies are highly justified for VHR patients. Alternatively, if other means are not available, VHR relapse children can just be treated as per the IEMC arm (isolated extramedullary relapses with CNS involvement) or the HR arm (all other relapses) both followed by SCT.

6. Salvage options

We suggest considering a shift to ‘Salvage options’ from the standard treatment backbones in the following situations:

- after HI, ≥ 5% blasts in marrow;
- after SI: residual extramedullary leukaemia;
- after SC1 or HC1, marrow ≥ 1% MRD or residual extramedullary leukaemia;
- after later time points ≥ 0.1% marrow MRD or residual extramedullary disease are identified;
- MRD reappearance ≥ 0.1% after previous molecular remission.

We recommend submitting these cases for discussion at the ALL-IC REL Tumour Board.

These cut off values are arbitrary and only stand here as approximate recommendations. The decision to continue on the original treatment backbone or to switch to salvage options should be carefully assessed by the treating physician-team. E.g. when a blinatumomab cycle is near down the line anyway, then it probably doesn't make sense to leave the original backbone due to a low level of residual marrow disease.

Arranging funds and permissions to administer blinatumomab or inotuzumab may be timely. In many countries, the time of a full chemotherapy cycle is needed for this, so the drug can only be given a cycle later than the decision which had been made to mandate its use. If so, it's worth considering the initiation of these arrangements to prepare for later administration of immunotherapies if:

- after SI or HI, marrow > 1% leukaemia or overt CNS-leukaemia are detected;
- after SC1 or HC1, any marrow MRD is measured;
- if marrow MRD reappears during the course of therapy.

Bridging time to immunotherapy with a less toxic cycle may be better than proceeding with intensive chemotherapy. E.g. an SC2 or a HD-MTX cycle can be used.

Below, we give a set of points to support the treatment choice among salvage options. Alternatively, these patients are encouraged to participate in early phase clinical trials.

<u>Inotuzumab (INO)</u> for B-cell precursor immunophenotype.
Follow the drug label re. administration.

- only if CD22 expression is demonstrated on blasts;
- 1st choice if marrow blasts ≥ 5%;
- may repeat INO cycles if response is observed;
- avoid in relevant liver toxicity;
- avoid if SCT is planned and similarly good options are available; best to insert INO earlier in the sequence of cycles if SCT is planned in order to reduce the risk of SOS (sinusoidal obstruction syndrome, alias VOD)
- do not repeat INO if MRD negativity is achieved, this is due to SOS risk during SCT.

<u>Blinatumomab (BLINA)</u> for B-cell precursor immunophenotype.
Administer as described in the ALL AIEOP-BFM 2017 protocol or as described in the CCLG 2021 UK Relapsed ALL Guideline v 1.3 or follow the drug label.
Considerations:

- only if blasts are CD19 pos;
- 1st choice if marrow blasts < 5%;
- 1st choice if severe infectious adverse events contraindicate myelotoxic chemotherapy (e.g. invasive fungal infection);
- contraindicated if CSF WBC > 5/ul or CNS infiltration seen radiologically;
- may repeat BLINA cycles;

- ideally, do not repeat BLINA cycles if MRD negativity is achieved and SCT is readily available (loss of MRD negativity occured in 6% of patients in the COG study);
- ideally, avoid blina if you plan to use CAR-T later (both are anti-CD19 immunotherapies) and you have similarly good treatment choices.

FLA(IDA) with or without peg-asparaginase for any immunophenotype.
To be given as per the ALLTogether protocol High Risk Block C1 or as per the Pediatric Relapsed AML 2010/01 protocol.
Considerations:

- first choice if the above immunotherapies can't be given (e.g. due to contraindications or no target CD markers or lack of funding/availability);
- first choice for patients with overt CNS disease (both fludarabine and HD-cytarabine penetrate the blood-brain-barrier)
- this toxic cycle may be repeated maximum twice more.

Nelarabine (NELAR) for T-ALL:
May be added in front of HC1/2/3 cycles as per ALL-IC REL 2016 protocol appendix.
Considerations:

- thought to improve treatment efficacy in T-ALL;
- choice especially in treatment resistant CNS disease as nelarabine penetrates the blood-brain-barrier.

VANDA for any immunophenotype
Administer as described in the COPRALL-2007 protocol or the PINDA Recaida Leucemia Linfoblastica Aguda 04.13. (2013) protocol.
Considerations:

- option for SR arm patients who didn't receive mitoxantrone and didn't receive HC2
- very toxic cycle, one of the last resorts

The above cycles may be given after each other in various sequences as indicated if the patient has ongoing residual leukaemia. However, if the marrow MRD is < 0.1% and no extramedullary leukaemia remains, it is advised to proceed to SCT as soon as possible. MRD reappearance and on-treatment further relapse are frequent in patients with resistant disease after relapse.

Further, last resort options may be:

- venetoclax in T-ALL, especially if immature, either in monotherapy or in combination with chemotherapy – note that this drug penetrates the blood-brain-barrier;
- i.v. daratumumab, especially for T-ALL, either in monotherapy or in combination with chemotherapy (Cerrano et al. Haematologica 107(4):996- and oral abstract 10001 by Hogan et al. at the ASCO 2022 congress on the DELPHINUS study);
- HD-MTX as per osteosarcoma or B-NHL protocols (8-12 g/m2 in 3-6 hr-long infusion) e.g. in persistent CNS disease,
- HD-ARAC as per AML-BFM HAM cycle without mitoxantrone (3 doses of 3g/m2 over 3 hrs, given every 12 hrs) in persistent CNS disease,

- TVTC cycle for any immunophenotype, see Shukla et al., Pediatr Blood Cancer 2014 Mar;61(3):431-5, be aware of very high toxicity,
- i.v. or i.th. rituximab (if blasts are CD20 positive) or i.th. etoposide (as per brain tumour protocols)

Chemotherapy, monoclonal antibodies, the above salvage options used even in combinations are insufficient themselves to provide long term cure for poorly responding relapse patients, or even for well responding high risk relapses. Only cellular immunotherapies, that are SCT and/or CAR-T, are needed to offer a chance for long-term cure.

7. Indications of CAR-T therapy

At present, CAR-T therapy is not available in all ALL-IC countries. The points below are written for centres who have this choice.

Consider CAR-T therapy in early post-SCT CD19-positive relapses. A 2nd SCT may be an option in late consequent relapses, especially if different conditioning or donor selection from the previous SCT procedure of the same patient are possible to use, especially total body irradiation and haplo identical donor.

Relapses in patients who never underwent SCT before: standard care is SCT, not CAR-T. Among SCT-naïve patients, CAR-T therapy is only recommended in the following four points at present.

- CAR-T therapy is the best option for patients who can't reach deep remission after multiple treatment attempts and therefore can't proceed to SCT. The patient doesn't have to get into remission to start CAR-T therapy. Preparing and treating patients for CAR-T therapy needs a totally different approach from preparing and treating patients for SCT. It is advised to follow instructions of the CAR-T centre where the patient is planned to be transferred to.
- Consider CAR-T in patients with heavy toxicities that render the child ineligible for SCT. E.g., insufficiently controlled invasive fungal infection, heart failure, etc.
- Data suggest that CAR-T therapy is efficient against CNS disease, it may be a better option than SCT in CNS relapses that were difficult to control.
- VHR relapses, as discussed above.

Typically, CAR-T is viewed as definitive therapy and is not followed by further anti-leukaemic treatment. However, some subgroups may benefit from SCT post-CAR-T:

- poorest prognosis subgroups, e.g. those with t(17;19),
- those with early B-cell recovery or with molecular relapse post CAR-T.

8. Options in case of severe toxicities

The following treatment cycles may be used as bridging or as alternative therapy elements in patients who can't tolerate toxicities:

- Blinatumomab, inotuzumab
- SC2 cycle
- Nelarabine
- Capizzi MTX
- Classic 3-drug induction (steroid, vincristine, asparaginase)
- CAR-T

Closing remarks

This is a very quickly developing field. The information provided may become obsolete soon. An update on T-cell ALL relapse strategy is expected in the near future. Similarly, data are emerging that TKI sensitive relapses (Phil+ and ABL-class fusion) need less intensive chemotherapy. Results of early phase studies on targeted biological therapies and immunotherapies are expected. Responsible physicians are asked to keep trace of ongoing advancements and to seek expert advice when treating relapsed childhood ALL cases.

In June 2022, the ALL-IC REL Tumor Board was started. This is a monthly online meeting of paediatric haematologists mostly but not exclusively from ALL-IC centres. This forum may help with advice re. treatment of R/R ALL patients and with informing participants in the most recent advancements of the field.

Irrespective of the available/lacking resources, or deviations from the protocol due to toxicities or other professional reasons or even mistakes, we ask all ALL-IC centres and even non-ALL-IC centres where this guidance is used to feed their cases into the ALL-IC REL registry. This will help us improve the guidance and gain knowledge to spread it again and again, for the patients' benefit. A new version of the registry is being prepared to accommodate diverse treatment journeys.

Please follow updates of this guidance at:
https://semmelweis.hu/gyermekklinika2/en/researches/all-ic/