Highlights in acute lymphoblastic leukaemia

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SUMMARY

The EHA congress is not only the opportunity to present or update the results of clinical trials, but it is also the occasion to present some fundamental research and to discuss certain themes that allow us rethinking the overall treatment strategy and monitoring of haematologic diseases.

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CHEMO-FREE REGIMEN FOR PH+ ALL

N. Short (MD Anderson) updated on the phase II trial investigating the chemotherapy-free combination of blinatumomab + ponatinib in newly diagnosed or R/R Ph+ ALL and in lymphoid blast crisis CML adult patients (N= 35). Previous therapy with one or two courses of chemotherapy +/- TKI was allowed in the newly diagnosed cohort. A complete molecular response is achieved in 17/20 (85%) of first-line patients, 7/8 (88%) of R-R and 2/5 (40%) of LBC-CML. With a median FU of twelve months (range, 1-37), the two-year EFS and OS of the frontline cohort is 93% with no relapse and no SCT. These impressive results certainly prompt us rethinking the induction strategy and perhaps the risk-benefit balance of allogeneic transplantation for certain Ph+ ALL patients. However, we must take into account the cost of such an association, short and long-term cardiovascular side effects and the biology of the disease if we are to put in place a strategy aimed at a cure.[1]

SOME HOPE FOR RELAPSING T-ALL

There has been quite a bit of discussion around T-ALLs. During an educational session, *D. Teachey (Children's Hospital of Philadelphia)* discussed potential new therapeutic agents based on T-ALL biology.[2] It is particularly relevant in the challenging situation of T-ALL relapse since, contrary to the situation of relapsing BCP-ALL where we have effective salvage treatments (inotuzumab, blinatumomab, CAR-T cells), in T-ALL relapse, apart from nelarabine, we don't have many valid therapeutic alternatives to offer.

At the end of the talk, he mentioned the **HEM-ismart study** further developed by *J.P. Bourquin (Zürich)* during a Scientific Working Groups session of the EWALL. This is a basket trial, which is starting in Europe and where patients who have a T-ALL relapse will get a comprehensive molecular profiling and an *ex vivo* drug reading. Based on the results of molecular signature and *ex vivo* profile they are allocated to a number of different arms looking at a number of different molecular targeting agents, including using venetoclax and navitoclax, a dasatinib based, a ruxolitinib based and a trametinib based regimen. Patients who do not have an underlying molecular lesion are eligible for a CD38 and CD47 antibody.

The approach looks very attractive but very realistically, *J.P. Bourquin* insisted on the fact that we must refrain on hype! There is a lot of uncertainty and this requires structured care based on an international leukaemia board. However, this kind of non-randomised trial is justified on the one hand by the catastrophic prognosis of patients with relapsing T-ALL and on the other hand by the accumulation of case-reports of patients whose completely chemoresistant disease is put back into remission using a therapy rationally targeting a signalling pathway which has been shown to be involved in the maintenance of the malignant phenotype.[3]

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It is also a response to the difficulty of organising comparative studies for rare diseases (such as subgroups of relapsed T-ALL). It will be necessary to judge the results of the global strategy and rethink the way of obtaining reimbursement for these targeted therapies, if successfully.

BETTER USE OF ALREADY AVAILABLE DRUGS

B. Vervoort (Princess Maxima Centre for Paediatric Oncology, The Netherlands) presented interesting data showing that loss of IKZF1 contributes to **cytarabine** resistance in BCP-ALL. Heterozygous loss of IKZF1 occurs in 10-15% of BCP-ALL and is associated to a higher incidence of relapse. It is already known that IKZF1 deletions cause resistance to glucocorticoids. Cytidine Deaminase (CDA) converts AraC in an inactive form. They demonstrated that IKZF1 normally inhibits CDA activity and that, upon loss of IKZF1, CDA expression is increased, resulting in resistance. As IKZF1 deleted tumour cells show selective sensitivity to different other antimetabolites like clofarabine or cladribine, tailored therapy with alternative antimetabolites may further improve outcome of this subgroup.[4]

SYNERGIES FOR LESS TOXICITY AND MORE EFFICIENCY

Another interesting talk from the Princess Maxima Centre for Paediatric Oncology research group was given by *M. Bulter* during the oral session 'ALL - signalling and beyond'. In an attempt to identify modifiers of **asparaginase** cell response, they identified the tyrosine kinase BTK and were able to demonstrate that BTK inhibition sensitises ALL to asparaginase by interfering with the amino acid response pathway, a pro-survival route that leads cells to quiescence, rather than towards apoptosis.[5] Normally, in the presence of BTK, asparaginase depletion leads to the activation of GCN2. Then, GCN2 can, in the presence of MYC, activate the amino acid response pathway so that cells can go to quiescence surviving the treatment. However, if BTK is supressed this escape mechanism is disturbed and cannot longer activate this pro-survival route, inducing cell death.

These data are particularly relevant. Indeed, asparaginase is a highly pertinent drug for ALL management but also a very toxic drug hard to handle, especially in the holder population of ALL patients. The optimised use of asparaginase is a cornerstone of successful administration of multi-agent chemotherapy.

With the arrest of production of *E. Coli* native asparaginase, clinicians are facing a challenging imposed situation where they must quickly learn to switch from a short-acting formulation to Peg-asparaginase, a long-acting formulation. The latter has many advantages in terms of treatment deviations and allergies, resulting in more efficiency. Peg-asparaginase has been extensively studied in the paediatric population and to a lesser extent in young adults. However, there is little data concerning its use in the 'older' adult population. The longer half-life time of peg-asparaginase allows less agility in case of toxicity so that the steering is more complicated.

A sponsored session was dedicated to the management of PEG-asparaginase toxicities, during which *N. Gökbuget (Goethe University, Frankfurt)* discussed with peers the subtly baptised 'modern' asparaginase options. She concluded that the drug was not so well tolerated in older patients in induction but manageable in consolidation. This forces to review induction schemes of the therapeutic adult protocols that are still using short-acting asparaginase in their backbone. This introduces an additional variable during the elaboration and comparison of protocols. *N. Gökbuget* also insisted that the balance between intended intensification and risk of toxicities requires individualised approach and experience. Management recommendations and continuous education of teams are crucial.[6]

THE BEAUTIFUL STORY OF CML-LIKE LEUKAEMIAS

During a 'spotlight talk' session, *Jan Zuna (Charles University Prague)* nicely told the story of CML-like leukaemias. It starts from the observation that while the correlation between the results of TEL-AML1 or MLL rearrangements transcript based minimal residual disease (MRD) with IGTCR based MRD was always over 90%, it was much lower when correlating BCR-ABL1 transcript based MRD with IGTCR based MRD. Particularly there were samples BCR-ABL1 positive even at high levels but IGTCR negative (discordant cases). By sorting different cell populations, they could demonstrate that in some patients, BCR-ABL1 was present also in non-leukaemic cells including T-cells and myeloid cells that are IGTCR negative. By monitoring the BCR-ABL1 fusion at the genomic level, they confirmed the discordance in 20-25% of paediatric Ph+ ALL samples. They also showed that IKZF1 deletions, that are the most common secondary aberrations in Ph+ ALL, mirrored the levels of IGTCR. They finally could demonstrate that in the concordant cases, the BCR-ABL1 fusion emerges in a committed B lymphoid progenitor and the resulting leukaemia cells with clonal IGTCR rearrangement, and possibly IKZF1 deletion, are then very homogeneous (typical ALL). In the discordant cases, the BCR-ABL1 fusion originates in a multipotent progenitor and the fusion is then present in

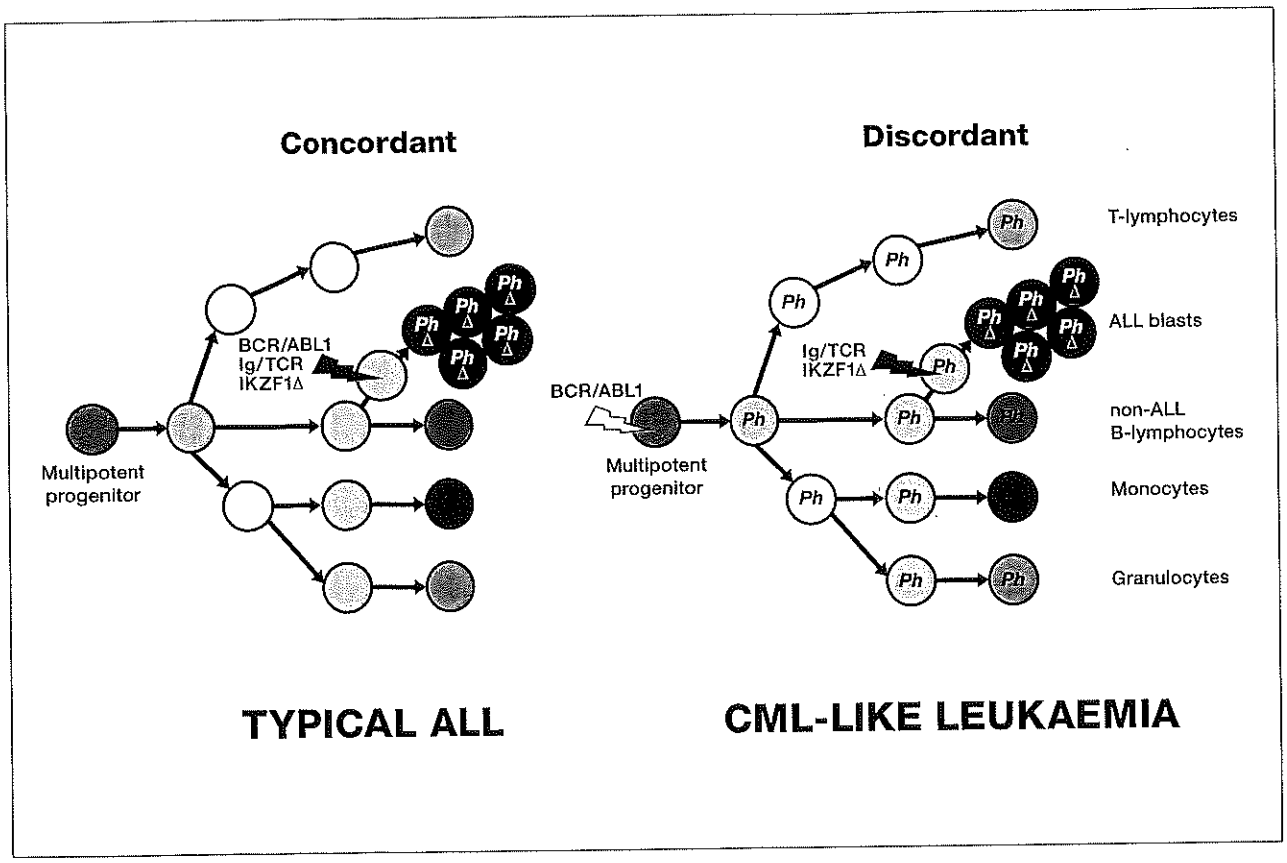

FIGURE 1. Typical ALL and CML-like leukaemia.[7]

various haematopoietic lineages. Some secondary events, possibly an IKZF1 deletion, then trigger acute leukaemia manifestation of the overt leukaemia with discordant results of MRD monitoring by BCR-ABL1 and IGTCR or IKZF1 deletion quantification. For biological similarity to lymphoid blast crisis of CML, they assigned those cases as CML-like leukaemias (*Figure 1*).[7]

This is an interesting story which illustrates the subtleties in the interpretation of the results of MRD, which can have important therapeutic implications, in particular in term of decision to allograft, or not.

CAR-T CELLS FOR T-ALL WITHOUT FRATRICIDE?

Yea Tan (Beijing Boren Hospital) presented the first results obtained with donor-derived anti-CD7 CAR-T cells in T-ALL patients. This protocol was then intended for patients who had undergone prior SCT, and for patients who were eligible for and had potential donors, including haploidentical. The therapy was created with IntraBlock proprietary technology that uses an intracellular organelle-anchoring domain that retains CD7 to endoplasmic reticulum with the aim of preventing T-cell fratricidal killing during the manufacturing process. Twenty patients were included in this phase I (median age, 11 years; range, 2-43). They were heavily pre-treated (at least two lines of previous therapy; range, 2-4) and extramedullary diseases were common. Twelve patients (60%) had previously undergone haematopoietic stem cell transplantation. Median follow-up was 6.3 months (range, 4-9.2). Cytokine release syndrome occurred in 90% of patients including one grade 3 and one grade 4. Maximum grade 2 GVHD developed in twelve patients within 45 days of infusion. All patients but one responded to therapy (overall response rate of 95%). Seventeen patients (85%) had an MRD-negative complete response to therapy by day 30. Two patients had a partial response, one of whom discontinued the trial to pursue another treatment. Seven patients received subsequent HSCT. Six of them, as well as nine of the eleven other study participants who had an initial complete response to therapy remained alive and disease free as of last follow-up. There was one CD7 negative relapse.[8]

REFERENCES

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KEY MESSAGES FOR CLINICAL PRACTICE

1. Reducing the toxicity of treatments and increasing their effectiveness remains a priority research objective. The chemo-free regimen story for Ph+ ALL is one demonstrating example.
2. One of the ways to achieve this goal is to continue to invest in the search for synergies between new drugs and old ones. The synergy between BTK inhibitor and asparaginase reported by *M. Bulter* is a good example but still needs to be validated clinically.
3. Understanding the signalling pathways and molecular anomalies that are responsible for maintaining the malignant phenotype in the different subgroups of leukaemia should make it possible to add targeted therapies to our current treatment regimens, but also to withdraw or replace ineffective drugs in some given patients. The HEM-ismart protocol, presented by *JP Bourquin*, and the link between loss of IKZF1 and cytarabine resistance, reported by *B. Vervoort*, are promising illustrations.
4. Finally, more than ever we must make our authorities aware of the importance of ensuring the availability of effective drugs, even old ones. This is a major issue if we want to take advantage of the benefits of new ones.

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