EDITORIAL

Shaping the future of older patients with Philadelphia-negative lymphoblastic leukemia

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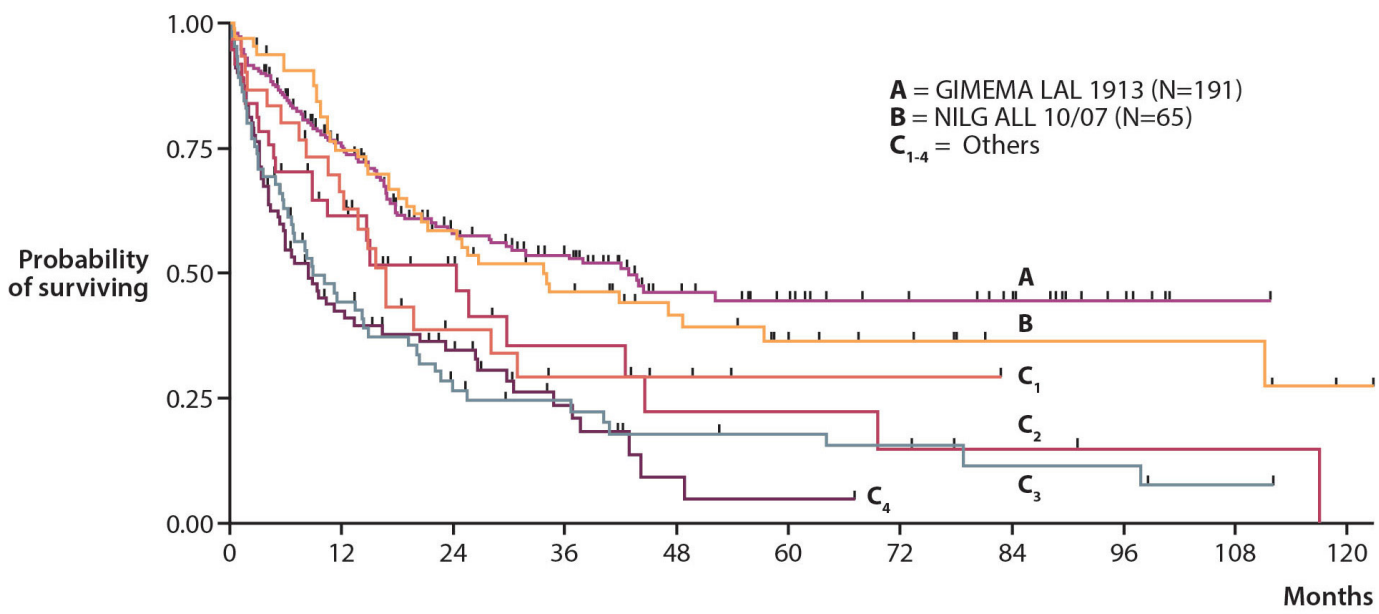
In this issue of *Haematologica* Cerrano and colleagues report on the outcomes of 476 patients aged 55-91 years (median 66 years) with Philadelphia-negative acute lymphoblastic leukemia (Ph^- ALL, N=455) or lymphoblastic lymphoma (N=21), who were treated between 2013-2023 with various chemotherapy regimens outside a prospective clinical trial.[1] The more frequently used protocols, totaling 256 patients, were two 'pediatric-inspired' chemotherapy programs with a minimal residual disease (MRD)-based risk stratification, which were originally applied to adults 18-65 years and differed only for a further drug dose reduction over 55 years and the use of pegaspargase in GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) LAL1913.[1] This commendable Campus ALL study assembled a large retrospective series of real-life patients with an extensive follow-up, integrating and corroborating the results of the two reference trials which included fewer patients aged 55-65 years and none above this range. The study provided clear evidence of the significant prognostic improvement achievable in Ph^- ALL patients aged 55+ years with age-modified 'pediatric-inspired' protocols, as already demonstrated by others[2] and by population-based surveys.[3] In this real-life analysis the cumulative complete remission (CR) rate was 76%, and 3-year overall survival and relapse-free survival were both projected at 40%. With NILG (Northern Italy Leukemia Group) 10/07- and GIMEMA 1913-type protocols survival rose to 50% and was still around 40% at 5 years (Figure 1A). These results rank among the best available for this unfavorable subset of patients,[2] although it is noted that blinatumomab or inotuzumab ozogamicin (InO) immunotherapy was used in about one fifth of all 256 study patients because of MRD persistence or resistance/relapse. Outcome was further improved in patients 55-70 years, in MRD-negative ones, and in those transplanted in first CR because of high-risk classification. The latter experienced a remarkable 3-year overall survival of 64%, in line with a recent joint European analysis.[4]

Although recognizing a certain therapeutic progress, the other side of the coin is that current standards do not prevent death from disease or treatment toxicity in one half or more of these patients, particularly when considering older ones and those with comorbidities. This critical issue elicited frontline immunotherapy trials with blinatumomab and/or InO, to define new standards of care for B-ALL. The main objective of the new immunotherapy-based trials has been to increase both CR and survival rates by lowering, at the same time, the risk of chemotherapy-related mortality (on average 30%, with wide ranges) through a marked downmodulation of its intensity, and that of relapse, to which most CR patients are exposed in chemotherapy-only programs. The immunotherapy studies so far published, including a single phase III trial (ECOG-ACRIN 1910) fulfilled these hopes, reporting outstanding CR and short-term survival figures compared to historical data (Table 1). Two other ongoing phase III trials aim to define new standards of care, comparing the efficacy of blinatumomab alternating with low-intensity chemotherapy *versus* standard chemotherapy in patients aged 55+ years (NCT04994717), and of InO with low-intensity chemotherapy *versus* standard chemotherapy, followed by blinatumomab and maintenance, in patients aged 50+ years (NCT05303792). Apart from stunning early results in the two immunotherapy trials with no or very little associated chemotherapy, SWOG 1318 and Alliance A041703, the survival probability decreased steadily over time after the second year of follow-up, without any clear evidence of a long-term survival plateau. This may be a warning for an immunotherapy-only post-remission approach when a prolonged survival at 3+ years is the goal. In fact, the patients in trials that combined chemo-immunotherapy consolidation (minimum of 4 blinatumomab cycles and 2 InO cycles) and maintenance were more likely to experience long-term overall and relapse-free surival rates around 60%, as did those younger than 70 years, MRD-negative patients,

or those having an allograft when suggested by their risk characteristics. And although induction toxicity was strikingly reduced in all immunotherapy trials, a high incidence of remission deaths (44%), often related to infections and secondary myeloid malignancies, was reported by a MD Anderson Hospital study associating both InO and blinatumomab plus rituximab (CD20$^+$ ALL) with low-dose chemotherapy.

Wishing to reach the maximum therapeutic benefit in patients over 55 years, we should turn our attention to some other factors that may play a role in the process (Figure 1B). First, adapting the definitions of performance status and fitness to non-intensive chemotherapy and targeting agents[5] could widen the access to age-adapted chemo-immunotherapy and allotransplantation too, increasing the transplantation rate of transplant-eligible patients, and in parallel explore other cellular therapies. Then, the sharing of an integrated risk score mainly based on post-induction MRD and ALL genetics, such as the one validated across different study groups,[6] would facilitate inter-study trials and large-scale comparative analyses on ALL subsets, risk groups and treatment elements, to better address some burning questions including allotransplantation in high genetic risk ALL turning MRD-negative after immunotherapy-based induction. Again, in the era of precision medicine, rapid and sensitive *ex vivo* drug re-

A **Overall survival according to treatment protocol in 476 real life older patients with Ph- ALL** (patient age 55-91 years; Campus ALL study 2013-2023)



B **Future incremental strategies of immunotherapy-based protocols for older patients with Ph- ALL** (current/future)

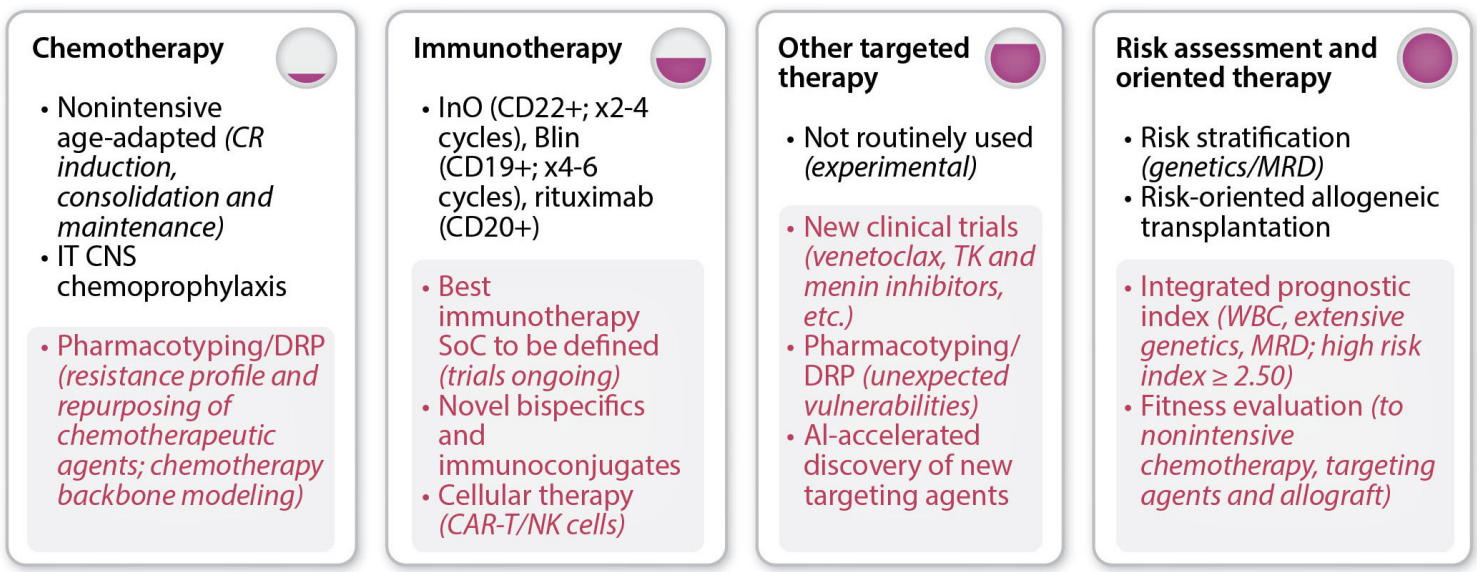


Figure 1. Survival of and treatment strategies for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. (A) Overall survival analysis by treatment protocol in 476 older adults with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph$^-$ ALL) (figure modified from *Online Supplementary Figure S1B* in the paper by Cerrano *et al.*[1]). (B) Future incremental strategies for immunotherapy-based protocols in older patients with Ph$^-$ ALL. CR: complete response; IT CNS: intrathecal administration for central nervous system disease; DRP: drug response profiling; InO: inotuzumab ozogamicin; Blin: blinatumomab; SoC: standard of care; CAR: chimeric antigen receptor; NK: natural killer; TK: tyrosine kinase; AI: artificial intelligence; MRD: minimal residual disease; WBC: white blood cell count.

Table 1. Main data and results from frontline immunotherapy studies with blinatumomab and/or inotuzumab ozogamicin in older adults with B-precursor acute lymphoblastic leukemia.

Study (first author, ref.)	N of patients; age, years, range (median)	Immunotherapy/ other therapy	CR %	MRD- negative, %	Outcome %	Notes
Blinatumomab-based						
ECOG-ACRIN 1910 (Litzow, N Engl J Med. 2024;391(4):320-333)	N=46 (MRD$^-$ CR) Age 55-70 (NA)	Blin x4 cycles (CONS) CHT (IND/CONS/ Maint)	-	-	3-y OS: 70 3-y RFS: 69	-Subset analysis of phase III trial patients 30-70 years in MRD$^-$ CR randomized to Blin (N=112) -Outcome significantly improved *vs*, no Blin arm -Safety: neurological Blin toxicity grade 3+ in 23% of 112 patients
GIMEMA 2317 (Bassan, Blood. 2025;145(21):2447-2459)	N=28 Age >55-65 (NA)	Blin x2 cycles (CONS) CHT (IND/CONS/ Maint)	68	92	3-y OS: 51 3-y EFS: 41 3-y RFS: 51	-Subset analysis on total study patients 18-65 years (N=149) -Safety: CHT-related IND mortality 25%; neurological Blin toxicity grade 3+ in 19% of 122 patients
SWOG 1318 (Advani, J Clin Oncol. 2022;40(14):1574-1582)	N=29 Age 66-84 (75)	Blin x1-2 cycles (IND), x3 cycles (CONS) CHT (Maint)	66	92	3-y OS: 37 3-y RFS: 37	-
GMALL BOLD (Goekbuget, Blood. 2023;142(suppl 1):964)	N=50 Age 56-76 (66)	Blin x4 cycles (IND/CONS) CHT (IND/CONS/ Maint)	85	82	1-y OS: 80 3-y OS: 67 3-y EFS: 60	-
Inotuzumab ozogamicin-based						
EWALL-INO (Chevallier, J Clin Oncol. 2024;42(36):4327-4341)	N=131 (CD22$^+$) Age 55-84 (68)	InO x2 cycles CHT (IND/CONS/ Maint)	88.5	80	1-y OS: 73 2-y OS: 55 1-y EFS: 64 2-y EFS: 46 1-y RFS: 66 2-y RFS: 50	-10 patients to allograft (2-y OS 90%) -Safety: VOD/SOS 1 patient
INITIAL-1 (Stelljes, J Clin Oncol. 2024;42(3):273-282)	N=43 (CD22$^+$) Age 56-80 (64)	InO x3 cycles (IND) Rituximab (CD20$^+$) CHT (CONS/ Maint)	100	71	1-y EFS: 88 3-y EFS: 55 1-y OS: 91 3-y OS: 73	-Safety: VOD/SOS 1 patient
Blinatumomab- and inotuzumab ozogamicin-based						
M.D. Anderson Cancer Center (Jabbour, Lancet Haematol. 2023;10(7):e490)	N=80 Age 63-72 (68)	InO x4 cycles (IND) Blin x4 cycles (CONS) Rituximab (CD20$^+$) Mini-hyper-CVD CHT (IND/CONS/ Maint)	99	94	2-y OS: 64 5-y OS: 46 2-y PFS: 58 5-y PFS: 44	-Blin since amendment (from patient 50), with InO reduction -CR: 7 patients with incomplete counts recovery -No outcome difference by Blin yes/no -Safety: 35 remission deaths (44%), with infection 8, MDS/ AML 9, VOD/SOS 4
Alliance A041703 (Wieduwilt, J Clin Oncol. 2025;43(32):3526-3535)	N=33 (CD22$^+$) Age 60-84 (71)	InO x1-2 cycles (IND), Blin x4-5 cycles (CONS)	85 (InO), 97 (InO+Blin)	91	1-y OS: 85 3-y OS: 60 1-y EFS: 75 3-y EFS: 45	-No further therapy after CONS -Safety: VOD/SOS 1 patient, encephalopathy 3 patients (1 fatal)

CR: complete response; MRD: minimal residual disease; ref.: reference; NA: not available; Blin: blinatumomab; CONS: consolidation; CHT: chemotherapy; IND: induction; Maint: maintenance; y: years; OS: overall survival; RFS: relapse-free survival; EFS: event-free survival; InO: inotuzumab ozogamicin; VOD/SOS: hepatic veno-occlusive disease/sinusoidal syndrome; PFS: progression-free survival; MDS/AML: myelodysplastic syndrome/acute myeloid leukemia.

sponse profiling techniques can enable the determination of the patterns of drug resistance or sensitivity to virtually all known antileukemic agents in both individual patients and ALL subsets, an endeavor globally referred to as pharmacotyping.[7] Pharmacotyping and drug response profiling assays correlate with 'omics'-based ALL subtyping and MRD status, and by disclosing drug resistance or unexpected vulnerabilities unrelated to disease genetics are better than 'omics' alone when looking for a rapid prediction of drug response from ALL blast cells.[8] Because of the high risk of chemoresistance and the poor chemotherapy tolerance displayed by older patients, pharmacotyping may identify the most suitable drugs for 'low-dose' immunotherapy-based regimens, be they traditional agents repurposed through drug response profiling or new targeting agents, also contributing to sparing unnecessary drug toxicity. Finally, new, more effective bispecifics, immunoconjugates and other targeting agents may become available soon, as a result of worldwide expansion of cancer immunotherapy research[9] and artificial intelligence-based, accelerated on-target compound screening programs.[10]

In summary the current prospects of immunotherapy for untreated ALL may be enlarged within a context increasingly oriented to involve aspects of precision medicine, to guarantee a better management of ALL patients and risk subsets, including T-ALL. These improvements should bring the survival of reasonably fit older patients with Ph$^-$ ALL consistently above 50% at 3+ years, with less concern about age limits, thereby gaining several life-years in good health in subjects whose life expectancy without a diagnosis of ALL is now about 80 years and more. Making all this possible is a highly demanding task, which will require joint efforts between ALL study groups and experts, scientific societies, regulatory authorities, national health and funding organizations, and pharmaceutical industries.

Disclosures

No conflicts of interest to disclose.

Contributions

RB and CS wrote and approved the manuscript.

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