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POSTER ABSTRACTS

612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

A Propensity Score Weighting Analysis Emphasizes the Progress of the Gimema Approach in Adult Ph-Positive Acute Lymphoblastic Leukemia in the TKI Era

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Introduction. In 2000, the GIMEMA cooperative study group launched the first frontline protocol with a tyrosine kinase inhibitor (TKI) alone plus steroids and without systemic chemotherapy for elderly (>60 years) Ph+ acute lymphoblastic leukemia (ALL) patients (LAL0201-B; Vignetti et al, Blood 2007). Thereafter, 4 academic clinical trials were conducted for adult patients (>18 years). In all studies, the induction was always based on a TKI alone plus steroids and CNS prophylaxis without systemic chemotherapy. In the GIMEMA LAL0904 trial, patients (18-60 years) received imatinib followed by chemotherapy in the post-induction phase (Chiaretti et al, Haematologica 2016). In the GIMEMA LAL1205 trial (no upper age limit), patients received dasatinib plus steroids, while the post-induction treatment was left to the investigator's choice (Foà et al, Blood 2011). In the GIMEMA LAL1509 total therapy protocol, patients (18-60 years) received dasatinib plus steroids followed by dasatinib alone in patients in complete molecular response (CMR) or chemotherapy and/or allogeneic transplant for those who did not reach a CMR (Chiaretti et al, Haematologica 2021). In the last LAL2116 trial, dasatinib plus glucocorticoids were administered in induction followed by at least two blinatumomab cycles as consolidation (Foà et al, N Engl J Med 2020). The rates of hematologic CR were comparable in the four trials, ranging from 96 to 100%.

Methods. In order to perform a reliable comparison, patient-level data from the Ph+ ALL patients enrolled in the LAL0904 (n=51), LAL1205 (n=63), LAL1509 (n=60) and LAL2116 (n=63) protocols were used to conduct a multilevel propensity score weighting analysis. The median follow-up was similar in LAL0904, LAL1509 and LAL2116 - namely, 51.8, 57.4, 52.9 months - while LAL1205 had a shorter follow-up of 24.8 months, due to the trial design. Survival estimates were thus calculated at 24 months, representing the minimum median follow-up within the 4 trials. The weights were calculated with a multinomial logistic regression model. The variables age at diagnosis, gender, WBC, *BCR::ABL1* isoform and allogenic transplant rate were included in this propensity score model. Differences in MRD rates were computed after the TKI alone induction using the chisq test. Given that the post-remission strategy was not defined in all protocols, the comparison of post-induction MRD was not appropriate. Survival curves were compared by standard and pairwise log-rank test.

Results. Among the balancing weights methods, the matching weights produced the best balance, with standardized mean differences <0.2 for all variables. As shown in Table 1, before weighting the baseline features were uneven; upon weighting, the 4 cohorts were balanced in terms of age, gender, WBC, *BCR::ABL1* isoform and transplant rate. After weighting, the MRD negativity rates at the end of induction were as follows: LAL0904 0%, LAL1205 23.9%, LAL1509 18.4%, LAL2116 29% (p=0.0007), mostly sustained by the different effect of dasatinib vs imatinib on the early molecular clearance. Survival outcomes after weighting underlined the superiority of the LAL2116 approach in comparison with the other protocols and the worse outcome for patients treated according to the LAL1205 scheme, presumably due to the lack of a uniform post-induction strategy. Indeed, the OS at 24 months was 89.8% in LAL2116, 71.2% in LAL1509, 52.9% in LAL1205, 66.2% in LAL0904 (p=0.001). Likewise, DFS at 24 months was 84.3% in LAL2116, 53.7% in LAL1509, 32.4in LAL1205, 61.1% in LAL0904 (p=0.001).

Conclusions. By using a multilevel propensity score weighting approach, we were able to compare with statistical accuracy the results of 4 GIMEMA protocols for the frontline treatment of adult Ph+ ALL patients. After weighting, two results clearly emerged: on the one hand the markedly superior survival of patients enrolled in the LAL2116 protocol and on the other hand the unfavorable outcome of LAL1205. The marked improvement observed with the LAL2116 trial is ascribable to the consolidation strategy based on blinatumomab, since LAL2116 shared with the earlier LAL1509 and LAL1205 protocols the same induction strategy (dasatinib). It also appears evident that a center-specific post-induction strategy - as in LAL1205 - is not beneficial.

Disclosures Chiaretti: *Incyte:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Membership on an entity's Board of Directors or advisory committees. **Vignetti:** *Novartis:* Speakers Bureau; *AbbVie:* Honoraria; *Uvet:* Honoraria; *Dephaforum:* Honoraria; *ER Congressi:* Honoraria; *IQVIA:* Honoraria.

Table 1. Baseline characteristics of patients enrolled in the LAL0904, LAL1205, LAL1509, LAL2116 trials at baseline after matching.

	Characteristics before weighting					Characteristics after weighting				
Characteristics	LAL0904 N=51	LAL1205 N=53	LAL1509 N=60	LAL2116 N=63	p-value	LAL0904 N=51	LAL1205 N=53	LAL1509 N=60	LAL2116 N=63	p-value
Age, mean (SD)	43 (11)	52 (14)	40 (12)	53 (13)	**<0.001**	46 (10)	48 (13)	47 (10)	47 (12)	0.392
Sex (% *female*)	55%	53%	43%	54%	0.57	52%	55%	50%	51%	0.966
WBC, mean (SD)	68 (113)	32 (34)	29 (39)	20 (22)	**0.007**	30 (31)	37 (33)	36 (44)	28 (25)	0.392
BCR::ABL1 (%)					**<0.001**					0.981
P190	76%	25%	55%	65%		62%	57%	57%	60%	
P210	14%	62%	30%	27%		29%	32%	32%	30%	
P190/210	10%	13%	15%	8%		8%	11%	11%	10%	
Transplant rate (%)	51%	47%	37%	44%	0.47	55%	49%	47%	46%	0.804

Figure 1

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