Daratumumab with or without chemotherapy in relapsed and refractory acute lymphoblastic leukemia. A retrospective observational Campus ALL study

The anti-CD38 antibody daratumumab, currently approved for the treatment of patients with multiple myeloma, is also being explored for patients with acute lymphoblastic leukemia (ALL), whose blasts commonly express high levels of CD38.[1] Patients with relapsed or refractory (R/R) disease, as well as those with positive measurable residual disease (MRD) have consistently shown unfavorable outcomes and, especially for T-lineage ALL, therapeutic options beyond first-line treatment remain limited. Preclinical studies have demonstrated that daratumumab has significant activity in human xenograft models of ALL, both as a single agent and in combination with chemotherapy.[2-4] However, the clinical experience is so far very limited. A few case reports have suggested that daratumumab has anti-leukemic activity in R/R and MRD-positive ALL cases,[5-10] but the small numbers of patients and the positive-outcome bias, due to the propensity to publish mainly positive results, prevent any robust conclusions on the clinical impact of this drug in ALL.

We hereby report a retrospective, observational study performed in patients with R/R or MRD-positive ALL who received daratumumab in Italy in order to provide further information on the safety and efficacy of this drug in a real-life context. In this study we included adult and pediatric patients with R/R or MRD-positive T- or B-lineage ALL or lymphoblastic lymphoma, who received at least one dose of daratumumab between December 2018 and December 2020 at 17 Italian hematology centers. Data were retrospectively collected in an anonymous database. This study was performed in the context of the Campus ALL national framework and in agreement with the Declaration of Helsinki. Patients received daratumumab either off-label or in the context of a compassionate use program, kindly supported by Janssen-Cilag Spa.

Daratumumab was administered at the approved schedule for multiple myeloma (i.e., 16 mg/kg weekly for 8 doses, then every 2 weeks for 8 doses, then monthly until disease progression), either alone or in combination with chemotherapy. The co-primary endpoints were overall response rate and overall survival of patients after daratumumab. Additional endpoints were safety and bridge to allogeneic hematopoietic cell transplant (HCT) after daratumumab. Complete response was defined as a bone marrow blast count <5% without evidence of extramedullary manifestations, partial response was defined as a bone marrow blast count ≥5% and <25% with a reduction of leukemic involvement of at least 50%. For lymphoblastic lymphoma, the Lugano criteria were applied. MRD was monitored either by flow cytometry and/or by real-time quantitative polymerase chain reaction in centralized laboratories. The overall response rate was defined as the proportion of patients who obtained a partial response, a complete response or, only for patients who were MRD positive, MRD negativity. Any systemic anti-neoplastic treatment started at diagnosis or with R/R disease counted as a line of therapy, except for allogeneic HCT.

Survival was estimated using the Kaplan-Meier method and overall survival was calculated from the date of the first daratumumab infusion to the date of death or the last follow-up. The association of baseline variables with response was explored using the Fisher exact, χ^2 or Mann-Whitney test, as appropriate. The cut-off date for this analysis was March 31, 2021 and data were analyzed with STATA 12.1 software (Stata Corporation, College Station, TX, USA).

We included 20 patients (85% males) in the study. Thirteen had T-ALL, four had B-ALL, one had mixed phenotype acute leukemia and two had lymphoblastic lymphoma (B-lineage in 1, T-linage in the other); 11 patients were treated front-line according to the GIMEMA LAL1913 intensive pediatric-like protocol.[11] The patients' characteristics are summarized in Table 1.

Daratumumab was administered at a median time of 13 months after diagnosis and patients had received a median of three prior lines of therapy. The median age of the patients at the start of daratumumab treatment was 35 years (range, 8-73) and three patients were below the age of 18. Nine patients had already undergone an allogeneic HCT, with a median time from transplantation to daratumumab treatment of 6 months (range, 2-20). At the start of daratumumab treatment, 80% of patients had a bone marrow relapse, either isolated or with concomi-

Table 1. Patients' characteristics.

Variable	N. or median	% or range
Male sex	17	85
Type of ALL	18	80
T	13	65
ETP	4	20
B	4	20
MPAL	1	5
Type of LBL	2	10
T	1	5
B	1	5
Firstline treatment		
LAL-1913	11	55
Hyper-CVAD	3	15
AIEOP-BFM	4	20
Others (EWALL, BFM)	2	10
Allo-HCT before daratumumab	9	45
Lines of treatment before daratumumab	3	1 - 4
Age at daratumumab start, years	35	8 - 73
Below 18 years	3	15
Disease status at daratumumab start		
Isolated BM relapse	8	40
Extramedullary and BM	8	40
Extramedullary and MRD positivity	2	10
Extramedullary only	1	5
CR, MRD-positive	1	5
Disease characteristics at daratumumab start		
White blood cells, $x10^9$/L	3.34	0.1 - 39
Platelets, $x10^9$/L	34	1 - 233
Peripheral blood blasts, %	14	0 - 98
Bone marrow blasts, %	45	0 - 100
ECOG at daratumumab start	2	0 - 4
Concomitant chemotherapy	9	45
Time from diagnosis to daratumumab, months	13	7 - 28

ALL: acute lymphoblastic leukemia; ETP: early-T-precursor; MPAL: mixed phenotype acute leukemia; LBL: lymphoblastic lymphoma; allo-HCT: allogeneic hematopoietic cell transplant; BM: bone marrow; MRD: measurable residual disease; CR: complete response; ECOG: performance status according to the Eastern Cooperative Oncology Group scale.

tant extramedullary disease. Extramedullary sites involved were the lymph nodes in four patients, the central nervous system in three, the mediastinum in two, the breast in one and the gut in one. The median performance status according to the Eastern Cooperative Oncology Group (ECOG) was 2. Daratumumab was administered alone in 11 cases (in 1 case after a short dexamethasone pre-phase), while nine patients received concomitant chemotherapy (*Online Supplementary Table S1*).

The overall response rate was 20%, with two patients achieving a MRD-negative complete response, one a complete response with persistent MRD and one a partial response (Table 2). Patients responded after two to six infusions of daratumumab and the median time to response was 4 weeks. Three of the four responses were observed in patients with T-ALL, who were treated with daratumumab as a single agent. Two patients (both with T-ALL) were alive at the last follow-up, one patient died after relapse and one died of treatment-related complications after allogeneic HCT. The characteristics of the responding patients are summarized in *Online Supplementary Table S2*. Four patients (2 responders, 2 refractory) proceeded to allogeneic HCT after daratumumab.

Next, we explored the potential factors associated with response. Patients with a bone marrow hematologic relapse (P=0.013), lower platelet count (P=0.019) and higher circulating blast percentage (P=0.034) were less likely to respond, while those with a better ECOG performance status (P=0.019) and who had received fewer prior lines of therapy (P=0.022) responded better (Table 3). Consistently, bone marrow MRD positivity, with or without extramedullary involvement, was associated with a better overall response rate, without however the difference reaching statistical significance (P=0.088).

Finally, we evaluated the potential association of CD38 expression on lymphoblasts with response. Among the 18 evaluable cases, CD38 positivity and mean fluorescence intensity did not differ significantly between responders and non-responders (median 96.5% *vs.* 95.6%, P=0.9 and 16,800 *vs.* 12,800; P=0.51, respectively)

At the last follow-up, all but one patient had stopped treatment and two patients remained alive and in complete remission. The median overall survival of the whole cohort was 4 weeks, with a 3-month overall survival rate of 25% (*Online Supplementary Figure S1*). No unexpected toxicities were observed and there was only one grade 2 infusion reaction.

Table 2. Outcome after daratumumab treatment.

Outcome	N. or median	% or range
Response to daratumumab		
Responders	4	20
CR, MRD-negative	2	10
CR, MRD-positive	1	5
PR	1	5
Non-responders	16	80
Stable disease	2	10
Progressive disease	12	60
Not evaluable	2	10
Allo-HCT post-daratumumab	4	20
in CR/PR	2	10
Treatment duration, weeks	2	2-120
Discontinued treatment	19	95

CR: complete remission; MRD: measurable residual disease; PR: partial remission; Allo-HCT: allogeneic hematopoietic cell transplant.

To our knowledge, this is the largest series of ALL patients treated with daratumumab reported so far and further underlines the potential activity of this drug in R/R and MRD-positive cases.

While the advent of monoclonal antibodies and chimeric antigen receptor T-cell therapy is progressively changing the therapeutic scenario in B-lineage ALL, the approved treatment options for R/R and MRD-positive T-ALL remain unsatisfactory, as highlighted by the large prevalence of T-lineage diseases in our cohort (14/20 total patients). Nelarabine has been confirmed to be active in this setting,[12] but responses are short-lived and half of the patients are resistant to the drug. More recently, the AKR1C activated prodrug OBI3424[13] and the BCL-2 inhibitor venetoclax have been tested in R/R T-ALL, and the combination of venetoclax and navitoclax with chemotherapy appears particularly promising.[14] However, data on these new agents are still immature and new therapeutic approaches are urgently needed.

Following preclinical data and a few positive case reports, daratumumab has started to be used in patietns with advanced ALL without other therapeutic options, but data from unselected cohorts are lacking. In our series, in which we included all patients who received at

Table 3. Predictors of response to daratumumab.

Variable*	Number (%) or median (range) Responders	Non-responders	P=
Sex			1
Male	4 (23.5)	13 (76.5)	
Female	0 (0)	3 (100)	
Age, years	34 (25 - 45)	35.5 (8 - 73)	0.92
T-lineage	3 (21.4)	11 (78.6)	1
B-lineage	1 (20)	4 (80)	1
Lymphoblastic lymphoma	1 (50)	1 (50)	0.37
Extramedullary disease	2 (18.2)	9 (81.8)	1
BM MRD°	2 (66.7)	1 (33.7)	0.088
BM relapse	1 (6.2)	15 (93.8)	**0.013**
Previous allo-HCT	2 (22.2)	7 (77.8)	1
Previous lines of treatment			**0.022**
1	2 (100)	0 (0)	
2	1 (25)	3 (75)	
3	1 (9.1)	10 (90.9)	
4	0 (0)	3 (100)	
White blood cells, x10^9/L	3.36 (3 - 4.3)	4.66 (0.1 - 39.4)	0.91
Hemoglobin, g/dL	10 (10 - 11)	9.5 (8 - 13)	0.25
Platelets, x10^9/L	151 (70 - 233)	27 (1 - 199)	**0.019**
PB blasts, %	0 (0 - 0)	24 (0 - 98)	**0.034**
BM blasts, %	2 (0 - 78)	50 (1 - 100)	0.099
ECOG score			**0.019**
0	2 (100)	0 (0)	
1	2 (40)	3 (60)	
2	0	4 (100)	
3	0	7 (100)	
4	0	1 (100)	
Concomitant chemotherapy	1 (11.1)	8 (88.9)	0.37

*Disease status and patients' characteristics evaluated at the time of starting daratumumab therapy. °Includes the patient in complete remission with isolated measurable residual disease positivity and those with extramedullary relapse and measurable residual disease positivity in the bone marrow. Bold values denote statistical significance at the P<0.05 level. BM: bone marrow; MRD: measurable residual disease; Allo-HCT: allogeneic hematopoietic cell transplant; ECOG: performance status according to the Eastern Cooperative Oncology Group scale.

least one dose of the drug, we observed a relatively low overall response rate of 20% and limited survival. However, most patients were heavily pre-treated, with a poor ECOG performance status and a high disease burden. Indeed, several of these patients would be excluded from any clinical trial. Responses were obtained rapidly, after two to six infusions of the drug, either alone or in combination with chemotherapy, and interestingly also in cases with extramedullary disease. Although limited by the small numbers, we could analyze potential predictive factors of response to daratumumab. We observed that patients with a high ALL burden (i.e., those with a bone marrow hematologic relapse and circulating blasts) were unlikely to benefit from the treatment, while daratumumab proved to be effective in patients with a good performance status and less advanced disease. These findings are in agreement with the current literature, with positive case reports mostly describing patients treated for MRD positivity or with low disease burden and in good clinical conditions. Indeed, a better selection of patients, as well as earlier use of the compound (e.g., in MRD-positive cases) appear crucial to obtain meaningful results. We also evaluated CD38 expression on lymphoblasts before the start of daratumumab therapy and found no significant association with response. Sample investigation was not centralized and so this exploratory analysis was limited by the heterogeneity of antibodies and analytical techniques employed by different flow cytometry laboratories.

We observed a patient who responded to daratumumab despite high disease burden, but in this case the antibody was used in combination with chemotherapy. Recently, a case report outlined the feasibility of this approach,[15] which is currently being tested in a clinical trial evaluating daratumumab in combination with chemotherapy in younger ALL patents (NCT03384654). This strategy might be the best option in the presence of a full-blown relapse, but the best chemotherapy regimen to combine with daratumumab remains to be defined. Combinations with innovative drugs with promising activity in ALL, such as venetoclax or bortezomib,[16] could also be tested following the experience in multiple myeloma,[17] as these patients are often chemorefractory.

We could confirm the safety of daratumumab in the setting of ALL, with a lower than expected rate of infusion reactions compared to those occurring in multiple myeloma and no unexpected toxicities. Although limited by its retrospective nature and the heterogeneity of the patients, our study provided data that could help to design new clinical trials aimed at testing daratumumab in ALL and to selecting patients who may benefit more from its use.

In conclusion, our data confirm the potential activity and safety of daratumumab in R/R and MRD-positive ALL, and suggest that this compound should be possibly used earlier, rather than after several lines of salvage treatment. Further studies are needed to clarify whether daratumumab could be another game-changer in this disease.

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