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CASE REPORT

Case Report: CAR-T cells and subsequent maintenance with ponatinib in an adult Philadelphia acute lymphoblastic leukemia patient with hematological and extramedullary relapse after allogeneic stem cell transplantation

Filippo Antonio Canale[1,2] | Martina Pitea[1,2] | Caterina Alati[3] | Gaetana Porto[1,2] | Giulia Pratico[3] | Giovanna Utano[1,2] | Jessyca Germanò[3] | Lucrezia Imbalzano[1,2] | Anna Ferreri[1,2] | Chiara Verduci[1,2] | Ludovica Santoro[1,2] | Giorgia Policastro[1,2] | Barbara Loteta[1,2] | Marta Pugliese[1,2] | Massimo Martino[1,2]

[1]Stem Cell Transplantation and Cellular Therapies Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

[2]Stem Cell Transplantation Program CIC 587, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

[3]Hematology Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

Correspondence
Martina Pitea, Stem Cell Transplantation and Cellular Therapies Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy;
Email: martina.pitea@ospedalerc.it

Abstract

Relapsed or refractory (r/r) Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) still represent an unmet clinical need despite the new immune therapies available for these patients. We report the case of a Ph + ALL relapsed one year after allogeneic stem cell transplant. After one DLI was started CAR-T program with brexucabtageneautoleucel, using as bridging treatment ponatinib, vincristine and prednisone. Brexu-cel infusion was performed in 2023, without CRS or ICANS onset. One month after Brexu-cel infusion BM aspirate and CT-PET showed recovery of full donor chimerism, MRD negativity and complete metabolic remission. Subsequently was started maintenance with ponatinib: at last follow-up, the patient persisted in leukemia-free status. CAR-T cells represent the most powerful treatment for r/r Ph + ALL but there is no consensus about the optimal bridging strategy and also regarding the management algorithm during "post CAR-T phase". Here, we report the efficacy of ponatinib as a bridge to anti-CD19 CAR-T cell therapy and as post CAR-T maintenance. Our experience suggests that a preserving approach with TKI associated to low-dose chemotherapy can be the optimal bridging therapy prior to CAR-T and that an "MRD-guided" and "TKI-based" maintenance strategy can represent the best choice for Ph + ALL which satisfactorily responds to CAR-T.

KEYWORDS

B-lymphoblastic leukemia, CAR-T cells, Philadelphia chromosome, ponatinib

Novelty Statements

What is the new aspect of your work?

Exploring therapeutic strategies for bridge to CAR-T and as post CAR-T maintenance in patient with relapsed refractory Ph ± ALL.

What is the central finding of your work?

We report the efficacy of ponatinib both as bridge therapy and as post CAR-T maintenance therapy.

What is (or could be) the specific clinical relevance of your work?

Our experience suggests that a preserving approach with TKI associated to low-dose chemotherapy can be the optimal bridging therapy prior to CAR-T and that an "MRD-guided" and "TKI-based" maintenance strategy can represent the best choice for Ph ± ALL which satisfactorily respond to CAR-T.

1 | CASE

Allogeneic stem cell transplant (allo-SCT) remains the standard strategy for achieving long-term disease-free survival in adult patients with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL).[1] However, a significant proportion of them continue to fail to achieve long-term cure. The introduction of more potent tyrosine kinase inhibitors (TKIs)[2] and the recent development of effective monoclonal antibodies[3,4] have provided more options for treating relapsed or refractory (r/r) patients. Furthermore, the development of CAR T cells is an innovation in the treatment of r/r ALL.[5] The best treatment strategy for these patients will have to be worked out in the coming years.

We report the case of a 54-year-old female diagnosed with Ph + B-cell ALL in May 2021. She presented leukocytosis (WBC count 103 × 10^9/L) and massive bone marrow (BM) infiltrate of lymphoid blasts positive for CD10, CD19, and CD22. Chromosome analysis revealed an abnormal female karyotype 47 XY, t(9;22)(q34;q11), with der(22) in 16 metaphases and t(14;20) in other eight metaphases; fluorescence in situ hybridization (FISH) detected p190 positivity. CT scan showed multiple enlarged mediastinal and abdominal lymph nodes. After steroid pre-phase, we started a combined therapeutic strategy with dasatinib associated to four doses of Vincristine. The patient achieved hematologic remission and continued treatment with dasatinib. In October 2021, a BM aspirate for qRT-PCRmonitoring of BCR-ABL1 mRNA transcripts showed a MRD of 8 < 10^{-4}. On November 2021, the patient underwent an allo-SCT from a matched unrelated donor. Conditioning regimen consisted of thiotepa, busulfan and fludarabine. GvHD prophylaxis consisted of anti-human T-lymphocyte immunoglobulin, short-term methotrexate and cyclosporine. Day +30 post-transplant BM aspirate documented a CR with full donor chimerism, absence of Philadelphia p190 translocation on FISH and MRD negativity. Post-transplant course was complicated by SarsCov2 infection in September 2022. The patient never developed GvHD. Five months after transplant a BM aspirate showed molecular relapse with MRD positivity at 10^{-3}. Cyclosporine was discontinued and donor lymphocyte infusions (DLIs) were infused. Despite this strategy, in November 2022 a BM evaluation detected 7% blasts, and loss of full donor chimerism and one month later the patient progressed to an overt hematologic relapse with substitutive infiltrate of blasts (79% on flow cytometry) at BM aspirate. The patient also reported pain localized at the right hypochondrium and CT scan demonstrated multiple abdominal lymphadenopathies (Figure 1A, B). No central nervous system involvement was found, while blasts mutational analysis detected the presence of T315I plus several other kinase domain mutations. Given the refractory disease, patient was referred to anti-CD19 CAR-T cell program with compassionate use of brexucbatageneautoleucel (Brexu-cel, Tecartus; Kite), which at the time was EMA-approved but awaiting approval from AIFA. Lymphapheresis was made in early December 2022 (on day +60 from DLI and day −38 from CAR-T infusion) and then was started a bridging treatment with ponatinib, vincristine and prednisone. Brexu-cel infusion was performed in January 2023, after lymphodepletion with fludarabine 25 mg/m^2 for three days and cyclophosphamide

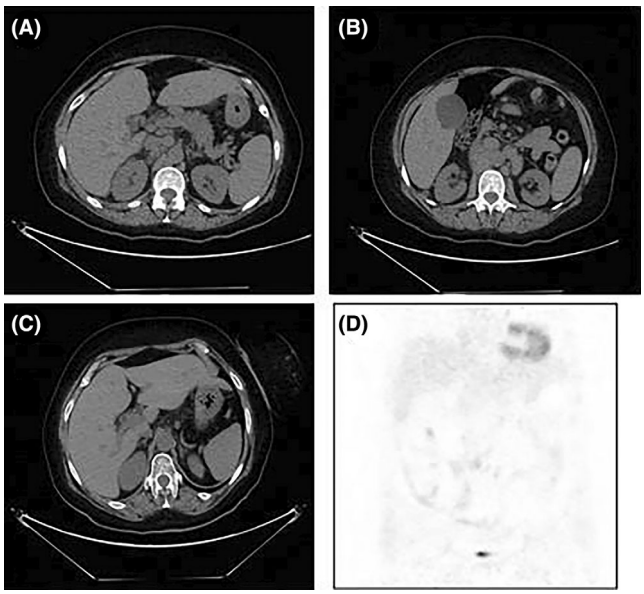

FIGURE 1 CT-scan at relapse post allo-SCT. (A) Enlarged lymphadenopathies localized near the hepatic hilum (major axis 36 mm). (B) Several retroperitoneal lymphadenomegalies. (C) Regression of abdominal lymphadenopathy by CT scan at day +90 after the infusion of brexu-cel. (D) Complete metabolic remissionby PET on day +90 after brexu-cel infusion (no high fluorodeoxyglucose uptake).

TABLE 1 Trend of blood count, bone marrow blast percentage, chimerism and measurable residual disease at three time points: lymphapheresis, day +30 after CAR-T infusion and day +90 after CAR-T infusion.

	Lymphapheresis	Day +30 car-t	Day +90 car-t
WBC $\times 10^9$/L	20.2	1.73	5.6
PLT $\times 10^9$/L	123	205	183
HGB G/L	104	101	126
BLAST	79%	0%	0%
CHIMERISM[a]	15% donor	100% donor	100% donor
MRD (RT-PCR)[b]	40.2	10^{-4}	Undetectable

Note: After brexu-cel the patient recovered full donor chimerism and reached MRD which became undetectable at day +90 during ponatinib maintenance.

[a]Chimerism evaluation using short tandem repeats analysis through simple polymerase chain reaction coupled with capillary electrophoresis (STR-PCR).

[b]MRD evaluation through BCR-ABL1:ABL1 ratio was measured by qRT-PCR.

900 mg/m^2 for one day. CAR-T cell treatment course was successful, without CRS or ICANS onset. One month after Brexu-cel infusion a BM evaluation showed a complete hematologic response, with a full donor chimerism and MRD negativity. PET and CT-scan confirmed complete remission of leukemia also in the extramedullary disease sites. To preserve this striking result, we started maintenance with ponatinib at a dose of 15 mg/day. Day +90 evaluation confirmed complete remission: absence of BCR-ABL1 transcript, clear dimensional reduction of lymphadenopathies with no radionuclide uptake, persistent full donor chimerism (Figure 1C, D and Table 1). At last follow-up, the patient was in good clinical condition and well-tolerated ponatinib maintenance therapy which is still ongoing.

r/r Ph + ALL is still a challenge despite the new immunotherapies available for these patients. Our case confirms the high efficacy of CAR-T cell, showing also that cellular therapy can restore full donor chimerism. Unquestionably CAR-T cells represent the most powerful treatment for r/r Ph + ALL but, to date, many issues in this regard have yet to be resolved. The first argument to define is which might be the optimal bridging strategy before CAR-T salvage. Here, we report efficacy of ponatinib combined with low-dose chemotherapy as a bridge to anti-CD19 CAR-T cell therapy. This strategy seems to be useful also in patients harboring TK domain mutations, as in our case. Another fundamental question is to establish a therapy algorithm for relapsed Ph + ALL during "post CAR-T phase." Indeed, there is no consensus regarding how to consolidate the response achieved with CAR-T cells. Notably, it should be considered that most patients undergoing CAR-T therapy have previously experienced a relapse post allo-SCT. Consequently, a transplant-based post CAR-T consolidation often means the execution of a second allo-SCT, which implies problems of excessive transplant-related toxicity. Therefore a meticulous balance between efficacy and safety should be mandatory, especially for subjects reaching MRD negativity after CAR-T. Regarding our case, once evaluated all the above concerns were chosen a "post CAR-T maintenance therapy" with lower-dose ponatinib, but if the patient had not previously undergone an allo-SCT we probably would have proceeded with it as a consolidation. The outstanding recovery of full donor chimerism after CAR-T therapy could derive from a "donor origin" of the engineered T-cells.

CAR-T cell products are approved for autologous use only: this is a problem for patients who experience ALL-relapse after allo-SCT, often showing circulating blasts. Donor-derived CAR-T cells represent an advantage for these patients, using a ready source of T-cells constituted by their original donors.

Regarding our case, we speculate that DLI prior to autologous lymphapheresis could be a good strategy to obtain "donor derived CAR-T" and therefore to enhance CAR-T efficacy after allo-SCT. This is one of the first reports of relapsed Ph + ALL in which ponatinib is fruitfully used both as a bridge and as maintenance after CAR-T cell therapy. In conclusion, we suggest that a "MRD-guided and TKI-based maintenance strategy" can represent the standard option for Ph + ALL which satisfactorily responds to CAR-T. Our experience seems also indicate that a preserving strategy with target treatment such as ponatinib associated to low-dose chemotherapy can be the optimal bridge prior to CAR-T for Ph + ALL.

AUTHOR CONTRIBUTIONS

Filippo Antonio Canale, Barbara Loteta, Anna Ferreri, Caterina Alati, Giulia Pratico, Marta Pugliese, Lucrezia Imbalzano, and Jessyca Germanò performed research; Gaetana Porto, Giorgia Policastro, Chiara Verduci, Ludovica Santoro, and Giovanna Utano performed data analysis; Filippo Antonio Canale, Martina Pitea, and Massimo Martino wrote the manuscript; Massimo Martino supervised the study. All authors approved the last version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Martina Pitea https://orcid.org/0000-0002-3982-4141

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