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Case Report

Long term outcome of a patient with relapsed refractory early thymic precursor acute lymphoblastic leukemia treated with daratumumab

Sachin Punatar[1,2], Anant Gokarn[1,2], Lingaraj Nayak[1,2], Avinash Bonda[1,2], Akanksha Chichra[1,2], Sumeet Mirgh[1,2], Bhausaheb Bagal[1,2], Prashant Tembhare[2,3], Papagudi Subramanian[2,3], Navin Khattry[1,2]

[1]HSCT Unit, Department of Medical Oncology Tata Memorial Centre, ACTREC, Kharghar, Navi Mumbai 410210, India; [2]Homi Bhabha National Institute (HBNI), Anushakti Nagar, Mumbai, India; [3]Department of Hematopathology, Tata Memorial Centre, ACTREC, Kharghar, Navi Mumbai 410210, India

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Abstract: The prognosis of patients with relapsed Early Thymic Precursor acute lymphoblastic leukemia (ETP-ALL) remains poor. Unlike B cell Precursor-ALL (BCP-ALL), there are no approved targeted therapies for ETP-ALL. Recent studies have identified a consistent expression of CD38 on the blasts of patients with T-ALL (both ETP-ALL and non ETP-ALL). Pre-clinical studies indicate that CD38 expression persists on the blasts of T-ALL even after receipt of conventional chemotherapy. These findings make CD38 an attractive targetable surface protein for patients with relapsed refractory T-ALL. We were the first to describe the clinical use of daratumumab in a patient of ETP-ALL, with relapsed disease post allogeneic transplant. We describe here the long term outcome of this patient more than 3 years after starting single agent daratumumab.

Keywords: Daratumumab, acute lymphoblastic leukemia, CD38

Introduction

Early thymic precursor (ETP) acute lymphoblastic leukemia (ALL) is a subtype of T-cell ALL with a poor prognosis. The presentation of ETP ALL is similar to other subtypes of T-ALL, but it has a distinct immunophenotype and genetic profile [1]. Also, it is characterized by chemo-resistance and has a poorer prognosis compared to other ALLs [2]. In particular, patients with relapsed or refractory ETP-ALL have a dismal outcome. These patients are often treated with salvage chemotherapy with or without transplant, but less than 10% of these patients have a long term survival [3]. These dismal outcomes are because the relapses are chemotherapy refractory and there are no standard targeted therapies available for these patients. Pre-clinical studies suggest that there is consistent expression of CD38 on blasts of patients with T-ALL; this expression is present at baseline, at relapse and persists even after conventional chemotherapy [4, 5]. These pre-clinical studies also demonstrate striking reduction in the disease burden in patient derived xenograft models of T-ALL, particularly ETP-ALL with daratumumab [4]. Therefore, CD38 seems to be a promising target for T-ALL, and daratumumab could be an effective therapy for relapsed refractory disease. We were the first to report successful use of daratumumab for a patient with post allogeneic transplant relapsed T-ALL [6]. We here describe the further course and the long term outcome of this patient following our initial publication.

Case report

Clinical history and treatment

The clinical history of this patient has been previously published [6] and also summarized in **Figure 1A**. The patient provided written consent for publication without identifying information. Briefly, this patient was diagnosed acute leukemia of ambiguous lineage in June 2013 when she was 26 years old. She relapsed within

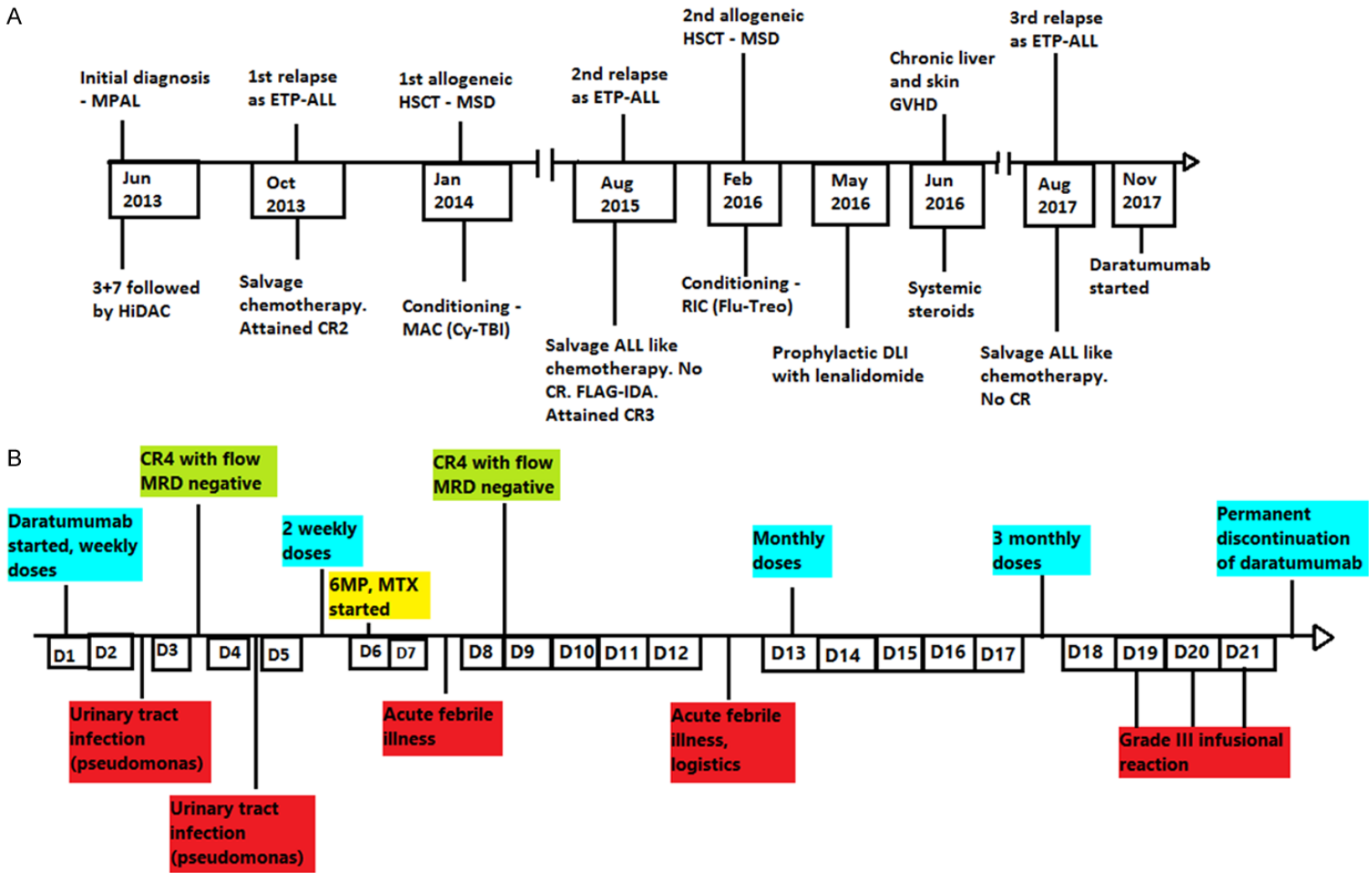

Figure 1. A. Clinical course prior to daratumumab. The major clinical events are shown above the line, and treatments below the line. (Abbreviations: MPAL-mixed phenotypic acute leukemia, HiDAC-high dose Ara-C, HSCT-hematopoietic stem cell transplant, MSD-matched sibling donor, MAC-myeloablative conditioning, Cy-TBI-cyclophosphamide with 13.2 Gy total body irradiation, FLAG IDA-fludarabine, ara-c, idarubicin with granulocyte colony stimulating factor, RIC-reduced intensity conditioning, Flu-Treo-Fludarabine with Treosulfan, DLI-donor lymphocyte infusion, other abbreviations as in text). B. Clinical course after start of daratumumab. The boxes in light blue indicate major daratumumab related decisions. Green boxes indicate disease assessment and yellow box additional therapy (excluding intrathecal therapy). Red boxes indicate toxicities. No space between two boxes indicates that the dose was given on time. Gap between boxes indicate delay. The reasons for delay are shown below the line. Intrathecal therapy is not shown for sake of maintaining clarity. (Abbreviations: 6MP-6 mercaptopurine, MTX-methotrexate, other abbreviations as in text).

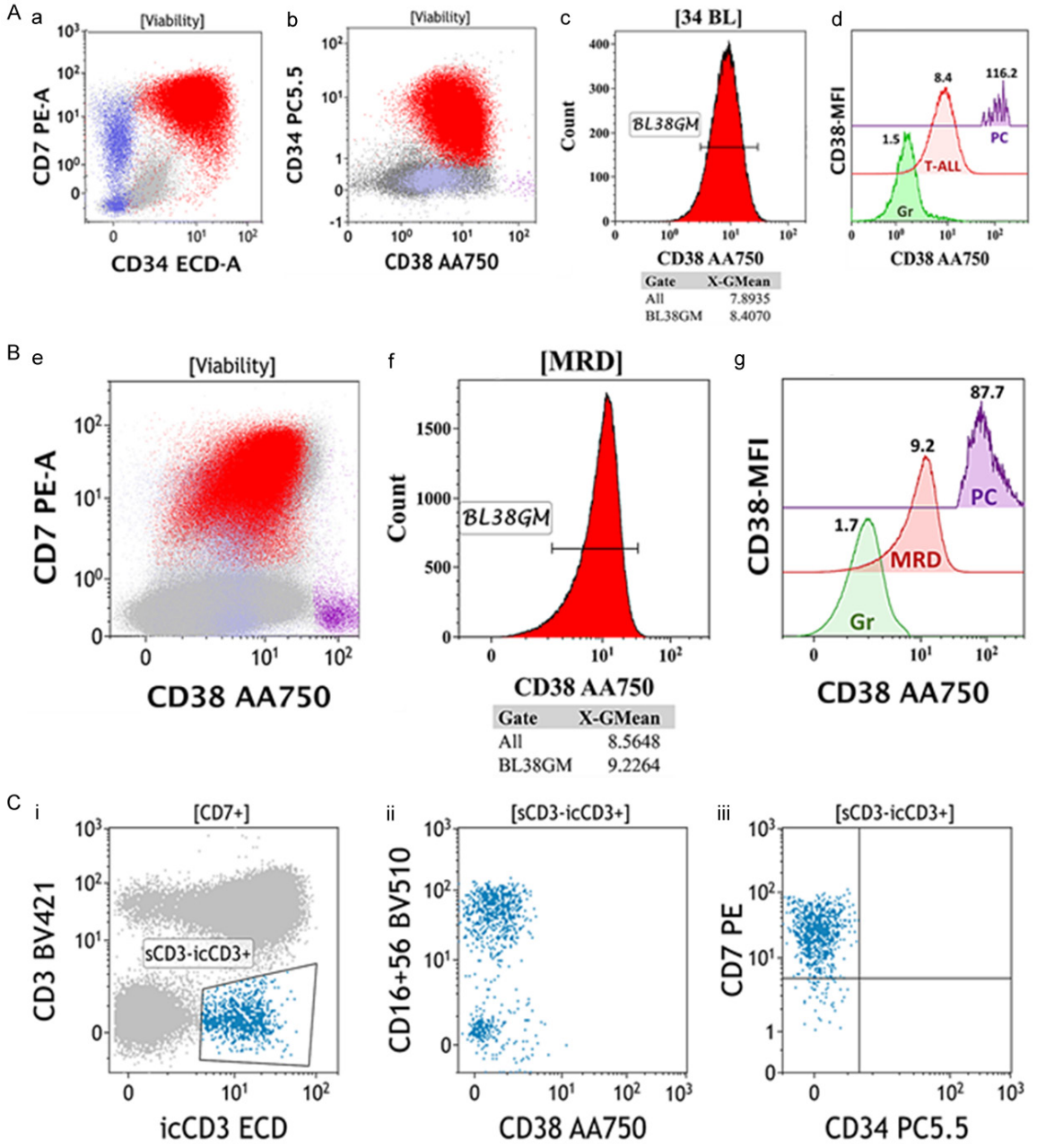

Figure 2. Flow cytometry plots at 3rd relapse (A, plots labelled a, b, c, d), post salvage chemotherapy but pre-daratumumab (B, plots labelled e, f, g) and after 3 doses of daratumumab (C, plots labelled i, ii, iii).

3 months of achieving 1st complete remission (CR1) with phenotype suggestive of ETP-ALL and underwent 1st allogeneic stem cell transplant (ASCT) from a matched sibling donor in 2nd complete remission (CR2). She relapsed after 21 months and then received a 2nd ASCT from another fully matched sibling donor in 3rd complete remission (CR3). Eighteen months from her 2nd transplant, she had her 3rd relapse. At her 3rd relapse (blasts intensely positive for CD38, CD34 and CD7, **Figure 2A**), she was treated with salvage chemotherapy containing dexamethasone, vincristine, pegylated L asparaginase and bortezomib, but did not attain remission (**Figure 2B**). In view of bright CD38 expression on the leukemic blasts, she received single agent daratumumab as an off label therapeutic indication.

Since no clinical studies/case reports were available at the time of initiating therapy with daratumumab, we chose to extrapolate the

dose and schedule as used in multiple myeloma. However, the plan had to be modified, due to toxicities. Only first 2 doses were given at weekly interval after which further doses were interrupted by recurrent infections (**Figure 1B**). After 5th dose, we decided to give daratumumab 2 weekly, monthly after 12th dose, and 3 monthly after 17th dose till 21st dose. The 19th to 21st doses were complicated by grade III infusional reactions and hence daratumumab was permanently discontinued.

Concurrent therapies

Since we did not have data about the central nervous system protection offered by daratumumab, we gave intrathecal methotrexate-initially weekly for 10 doses and subsequently, fortnightly for 7 doses. After 5 doses of daratumumab, we started 6-mercaptopurine (50 mg/m^2/day) and oral methotrexate (20 mg/m^2 weekly). Till date the patient continues to be on maintenance therapy with 6-mercaptopurine and weekly methotrexate.

Disease status and chimerism

Pre-daratumumab marrow showed 15.6% measurable residual disease (MRD) by flow cytometry (**Figure 2B**). The bone marrow chimerism showed 89% donor cells (by polymerase chain reaction analysis of variable nucleotide tandem repeats-VNTR). Concurrent peripheral blood chimerism was 100% donor. The first marrow study after start of daratumumab was done at 4 weeks. By then, 3 doses of daratumumab had been given. The marrow was in complete remission (CR4) with MRD negative by flow cytometry (**Figure 2C**). Bone marrow chimerism improved to 100%. After total of 8 doses of daratumumab, repeat marrow studies showed CR with MRD negativity with 100% donor chimerism. No further marrow studies have been required so far. All peripheral blood chimerism studies post-daratumumab have persistently shown full donor chimerism. She is now more than 16 months from permanent discontinuation of daratumumab (and more than 3.5 years from initial start of daratumumab) and remains in CR.

Toxicities

The tolerance to daratumumab was fair, with multiple dose delays due to infective complications. During the initial weekly and fortnightly doses, the patient had 4 episodes of bacterial infections-two urinary tract infections (both caused by multi-drug resistant pseudomonas aeruginosa) and 2 undifferentiated febrile illnesses of presumed bacterial origin. She had 1 episode of cytomegalovirus reactivation (after the 5th dose) with a low level viremia, and did not require any specific therapy. No fungal infections were observed. No de novo graft versus host disease (GVHD) or flare of previous chronic GVHD was observed. **Figure 1B** summarizes the clinical course after start of daratumumab.

Discussion

Daratumumab is an important recent addition to the armamentarium of drugs useful in myeloma. It has been used in myeloma as a single agent as well as in combination with other anti-myeloma drugs [7]. Apart from myeloma, preclinical studies have been conducted for the use of this drug in acute myeloid leukemia (AML) and ALL [4, 5, 8, 9]. Clinical cases of daratumumab in diseases other than myeloma have been restricted largely to ALL [6, 10-12]. These single centre reports followed after we reported the first patient of relapsed refractory ETP ALL who achieved MRD negative remission with daratumumab. Additionally, daratumumab has been used for post allogeneic stem cell transplant autoimmune hemolytic anemia [13] and post allogeneic transplant pure red cell aplasia [14].

Relapsed refractory ALL remains a clinical challenge, more so with T-ALL. With several cases reporting the successful use of daratumumab, this drug provides a novel therapeutic option. Although there are no large studies in ALL to guide dosing in ALL, all reported cases have used the standard dose of daratumumab as is used in myeloma [6, 10-12]. The dosing strategy and the duration of therapy in ALL are areas of open discussion. In some case reports, only a few doses were administered so as achieve remission [10-12], and followed by transplant. We however, used it for a relapse after 2 prior allogeneic transplants. Hence, similar to myeloma, we decided to use it till disease relapse or till unacceptable toxicity. In our patient, we discontinued daratumumab due to recurrent severe infusion reactions. Although infusional

reactions are very commonly described with the initial doses of daratumumab, it is unclear why they were seen after so many doses in our patient.

One of the concerns in using daratumumab prior to or after ASCT is the increased risk of GVHD. While no studies in ALL are available, about 15% of myeloma patients developed de-novo acute GVHD after daratumumab therapy for post ASCT disease relapse [15]. This might be due to its effects on several CD38 positive immune and other cells [16, 17]. Our patient did not develop acute or chronic GVHD after starting daratumumab.

The factors that would predict a long term benefit from daratumumab are not precisely known. Surface CD38 expression has been found to be an important factor in determining cell lysis in pre-clinical myeloma models [18]. Pre-clinical studies in ALL also indicate that intensity of surface CD38 expression on ALL blasts may impact benefit from daratumumab [4]. It is likely that the sustained benefit in our patient was due to the bright expression of CD38 on the leukemic blasts.

In summary, this is the first report of long term outcome of a patient with relapse-refractory ETP-ALL responding to daratumumab after 2 allogeneic transplants. Daratumumab likely will be an important therapeutic option in patients with T-ALL, particularly ETP-ALL. Further studies are necessary to find out its optimal place in the treatment of this disease which otherwise has relatively dismal prognosis.

Disclosure of conflict of interest

SP and PT have attended Janssen Oncology Advisory Board meetings twice. However, the honoraria from the meeting were paid to the institute and were subsequently transferred to a patient welfare charitable fund. At the time of the meetings, neither SP nor PT were authorized signatories to the aforementioned charitable fund. No personal honorariums were received by either of the authors. For rest of the authors-No conflicts of interests.

Address correspondence to: Dr. Navin Khattry, HSCT Unit, Department of Medical Oncology Tata Memorial Centre, ACTREC, Kharghar, Navi Mumbai 410210, India. Tel: 00919892501884; E-mail: nkhattry@gmail.com

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