Sequential therapy with inotuzumab ozogamicin, CD19 CAR T cells, and blinatumomab in an elderly patient with relapsed acute lymphoblastic leukemia

Ramona Wullenkord & Christian Reicherts & Jan-Henrik Mikesch & Julia Marx & Klaus Wethmar & Jörn Albring & Simon Call & Georg Lenz & Matthias Stelljes

Received: 29 June 2020 / Accepted: 18 August 2020

Dear Editor,

Whereas outcome in younger patients with acute B-lymphoblastic leukemia (B-ALL) improved over the last decades, prognosis for older patients, especially with relapsed or refractory (r/r) disease, remains particularly dismal [1, 2]. Novel targeted approaches including inotuzumab ozogamicin (InO), blinatumomab (Blina), and CD19-directed chimeric antigen receptor (CAR) T cells demonstrated promising efficacy in recent phase II/III trials [3–9]. Here, we report a case of an elderly patient with repeatedly relapsed ALL treated sequentially with InO, CD19-specific CAR T cells, and finally, with Blina for relapse after CAR T cell therapy.

In March 2017, a 73-year-old female patient was diagnosed with a precursor B-ALL. Flow cytometry showed 95% positivity for CD19 and CD22 surface antigens. First complete remission with no detection of minimal residual disease (MRD) was achieved after a first cycle of standard induction chemotherapy. After six additional cycles of chemotherapy, a molecular relapse occurred followed by an overt relapse in June 2018. The patient was treated with six cycles of InO, inducing a MRD-negative CR without relevant adverse events or alterations in quality of daily life. In March 2019, a second relapse occurred. Lymphocytes were harvested for autologous CAR T cell production within a clinical trial (NCT03853616). While waiting for the CAR T cell product, the patient progressed with symptomatic CNS involvement. Hence, further treatment continued off study and consisted of intrathecal chemotherapy and a further cycle of InO. Subsequently, a partial remission with no evidence of active CNS involvement could be achieved. After a lymphodepleting chemotherapy, the patient received CD19 CAR T cells without any complications or any impairment in quality of life. CAR T cell persistence in the peripheral blood was measurable until day 20 (Fig. 1). Remission control showed a third MRD-negative remission. Five months after CAR T cell therapy, MRD turned positive again, followed by a third overt relapse with involvement of bone marrow and CNS in December 2019. After clearance of blasts in the cerebrospinal fluid by intrathecal chemotherapy, the patient received Blina and achieved a fourth MRD-negative CR after the first cycle. Except mild neurological adverse reactions, treatment was well tolerated and continued for two additional cycles.

Treatment of r/r B-ALL in older patients remains a clinical challenge and is often based on individual decisions. Conventional salvage approaches with intensive chemotherapy (e.g., high-dose AraC ± mitoxantrone, fludarabine/AraC ± idarubicin) are not applicable for most older patients due to high toxicities. Moreover, two recently published randomized trials have shown inferior response rates and survival outcomes compared to novel immunotherapies [4, 6]. Allogeneic stem cell transplantation as consolidation for those patients achieving a CR is of particular importance with regard to long-term outcome. In older patients, this option is only possible in selected fit patients [10]. So far, data on CAR T cell therapy in older patients with B-precursor ALL and active CNS involvement are limited. In general, the observed CAR T cell-related toxicities such as cytokine release syndrome or neurologic toxicities in older patients seemed to be comparable in those seen in younger patients [11]. Our case report demonstrates efficacy and tolerability of CD19-directed CAR T cell therapy in an elderly patient with r/r B-ALL. Given the debulking capacity of InO and the distinct type of targeted antigen makes it rational to apply InO as a bridging therapy prior to CAR T cell application. For CD19+ relapses, Blina can be considered as effective salvage treatment, even after CAR T cell therapy. This case report demonstrates that novel immuno-salvage therapies represent an effective, safe, and...
feasible treatment option in older patients with r/r B-ALL without impairment of their quality of life. The optimal sequence of novel targeted therapies has to be defined in the future.

**Acknowledgments** Data on cell subset analyses after CAR T cell therapy were kindly provided by Miltenyi Biotec.

**Authors' contributions** M.S. R.W., C.R., J.-H.M., J.M., K.W., J.A., S.C., and G.L. were involved in the diagnostics and treatment of the patient. R.W. and M.S. wrote the manuscript and prepared the figure. All authors reviewed and approved the manuscript.

**Funding Information** Open Access funding provided by Projekt DEAL.

**Compliance with ethical standards**

**Conflict of interest** MS holds a consulting or advisory role at MSD, Amgen, and Pfizer; and received honoraria from Jazz Pharmaceuticals, Amgen, Novartis, and Pfizer; and research funding from Pfizer. The other authors declare that they have no conflict of interest.

**Ethics approval** n.a. (no clinical study).

**Consent to participate** Informed written consent of the patient for all therapies and research purposes.

**Consent for publication** Informed written consent for publication.

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