Lasting remission following multimodal treatment in a patient with metastatic breast cancer

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We report on a lasting remission from multimodal treatment in a patient with hepatic metastasized breast cancer. After surgical removal of a singular hepatic metastasis, the patient underwent leukapheresis of peripheral blood mononuclear cell (PBMCs). For induction chemotherapy, the patient received 2 cycles of epirubicin and paclitaxel (ET). After 1 cycle of epirubicin and ifosfamide (EI), peripheral blood stem cells were harvested. After a final cycle of ET, the patient underwent high-dose chemotherapy (HDCT; thiotepa 600 mg/m^2/ melphalan 180 mg/m^2) and autologous stem cell transplantation. Once reconstitution was achieved, PBMCs were reinfused followed by i.v. application of a trifunctional antibody (TrAb) with specificities anti-EpCAM × anti-CD3. TrAbs are able to simultaneously bind tumor cells, T cells, and additionally FcγR type I and III + accessory cells via their Fc region. Side-effects during treatment were hematotoxicity, mucositis and gastrointestinal toxicity. TrAb treatment resulted in intermittent fever, chills, elevated liver enzymes, systemic inflammatory response syndrome and pulmonary leakage. With a follow-up period of more than 8 years the patient is still in remission (96 + months). This case suggests the feasibility and efficacy of combining surgery, standard and HDCT, and subsequent immunotherapy in metastatic breast cancer. Further investigation of this approach is indicated in a subgroup of patients with oligometastatic breast cancer. ***Anti-Cancer Drugs*** **16:1135–1137 © 2005 Lippincott Williams & Wilkins.**

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Introduction

High-dose chemotherapy (HDCT) is able to increase the rates of objective responses in metastatic breast cancer (MBC) and event-free survival may be prolonged compared to conventional treatment [1,2]. Since Stadtmauer *et al.* found no impact on overall survival in a randomized trial comparing conventional and HDCT, they concluded that a single course of HDCT cannot be recommended routinely for women with MBC [2].

In a pilot study for patients with MBC, we investigated the use of immune reconstitution and activation of previously harvested autologous peripheral blood mononuclear cells (PBMCs) against tumor cells. PBMCs were collected prior to chemotherapy and all preparations were purged. After hematopoietic reconstitution, PBMCs were reinfused followed by treatment with a trifunctional antibody (TrAb) for activation and redirection of T cells and FcγR-positive accessory cells versus tumor cells (Fig. 1).

The present case reports the clinical course of a patient who was treated according to this study protocol for MBC.

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Case report

History

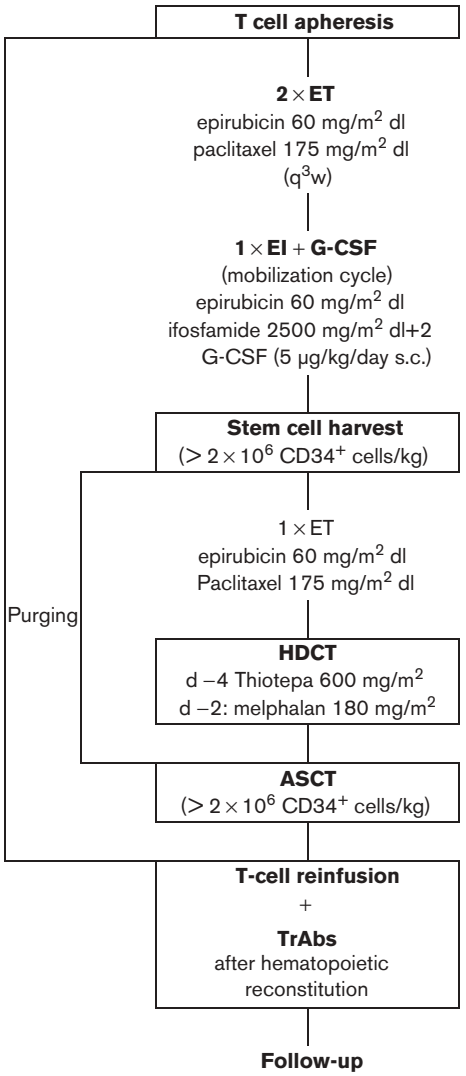
A 39-year-old woman was diagnosed with stage II breast cancer in September 1993 (pT2, pN0, M0, G2, ER/PgR$^-$, HER2$^-$). After mastectomy and axillary dissection the patient received 6 cycles of adjuvant cyclophosphamide/ methotrexate/5-fluroruracil (CMF). In November 1996, a metachronous, singular, hepatic metastasis was diagnosed, which could be surgically removed (R0). Immunohistochemical analyses showed an overexpression of the tumor-associated antigen EpCAM. Staging examinations excluded any other manifestations of the disease.

Due to a high risk of relapse, the patient gave written informed consent for treatment accordingly to a HDCT protocol for MBC approved by the local ethics committee.

Induction chemotherapy

First, the patient underwent an apheresis of PBMCs. All harvests (PBMCs and stem cells) were purged by using the MaxSep System which includes three murine

Fig. 1



Study design.

anti-human breast cancer antibodies (42 kD 9189, 55 kD 8187, 200 kD 9148; Baxter Immunotherapy, Unterschleisheim, Germany) and immunomagnetic beads (Dynabeads; Dynal, Olso, Norway). After cryopreservation of PBMCs, the patient received 2 cycles of ET (epirubicin 60 mg/m^2 day 1, paclitaxel 175 mg/m^2 day 1, q3w). To mobilize stem cells the patient received 1 cycle of epirubicin (60 mg/m^2 day 1) and ifosfamide (2.5 g/m^2 days 1 + 2 given as an 18-h infusion) followed by granulocyte colony-stimulating factor (G-CSF; 300 µg s.c. daily). A final cycle of ET was applied after leukapheresis.

HDCT

Myeloablative HDCT started on day −4, consisted of three 1-h infusions of thiotepa with 2 h rest between each dose (total dose 600 mg/m^2). Two days later (day −2) patients received three 1-h infusions of melphalan with 2 h rest between each dose (total dose 180 mg/m^2). Stem cells were reinfused on day 0 and G-CSF (5 µg/kg) was given to stimulate hematopoietic recovery. Hematopoietic reconstitution was achieved on day 9 after autologous stem cell transplantation (ASCT).

PBMC reinfusion and TrAbs

Autologous PBMCs were reinfused 2 weeks after reconstitution. TrAbs were given at a test dose of 10 µg 48 h after autologous PBMC reinfusion which was accompanied by fever. A second dose of 200 µg was administered 48 h later, which resulted in fever, chills and systemic inflammation response syndrome. The occurrence of progressive dyspnea and bilateral pulmonary infiltrates led to the diagnosis of pulmonary leakage, and the patient was transferred to the ICU. Intermittent administration of catecholamines was necessary, but the patient reconstituted without mechanical ventilation support by treatment with high-dose steroids within 72 h.

Results

With a follow-up period of more than 8 years the patient is still in remission without any evidence of disease (96 + months).

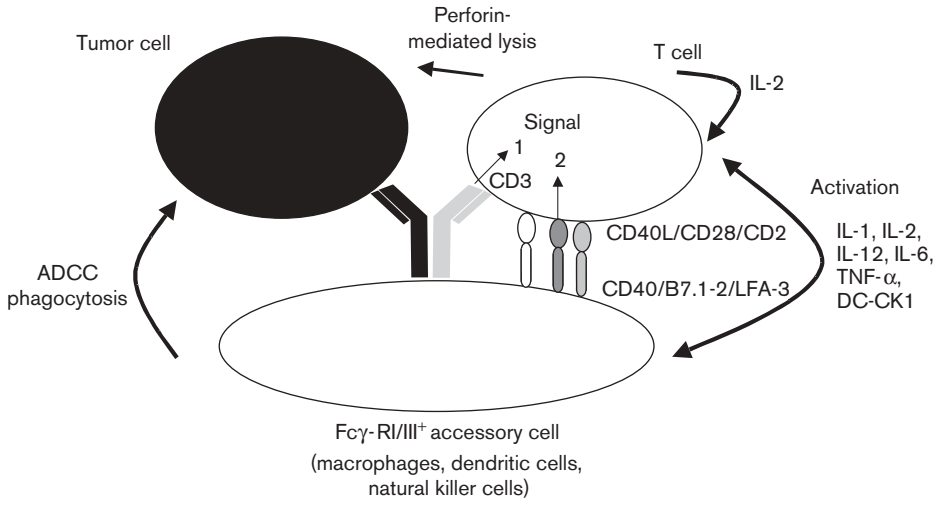
Discussion

HDCT is able to increase the rates of objective responses, but the influence on overall survival in randomized trials seems to be limited [1,2]. In contrast, Nieto *et al.* as well as other groups reported an unexpected long median survival time up to 80 months in oligometastatic breast cancer [3,4].

Since transient T cell immunodeficiency is a common complication following hematopoietic stem cell transplantation, rescue of T cell function by autologous T cells was expected to be beneficial for immunotherapeutic approaches [5]. In our own pilot study for MBC, this immunotherapeutic approach was included into the HDCT protocol (Fig. 1). Autologous PBMCs containing T cells collected prior to chemotherapy are reinfused together with a bispecific, trifunctional antibody (anti-EpCAM × anti-CD3). This experimental approach promises highly effective elimination of tumor cells by simultaneous redirection and activation of T cells via its anti-CD3-binding site and accessory cells (monocytes, macrophages, dendritic cells and/or natural killer cells) via its binding to FcγRs [6–9]. In this way, tumor cells are not only destroyed and removed by killer mechanisms, e.g. perforin-mediated lysis and phagocytosis, but T cells may also be activated specifically against the tumor (Fig. 2) [10].

The application of the second dose of TrAb (200 µg) was accompanied by considerable side-effects such as fever,

Fig. 2



The postulated three-cell complex. The trifunctional antibody is able to accelerate the recognition and destruction of tumor cells by different immune cells. ADCC: antibody dependent cell-mediated cytotoxicity; DC-CK1: dendritic cell cytokine 1; LFA: leukocyte function-associated antigen; TNF: tumor necrosis factor.

chills and increased liver enzymes, which is thought to be due the expression of EpCAM on the bile duct epithelium. Within 24 h after the infusion of TrAbs, the patient developed a systemic inflammatory response syndrome and was transferred to the ICU. Suspected pulmonary leakage was treated by high-dose steroids and all symptoms eased off within 72 h. TrAb doses for further recruited patients were therefore given in three escalating dose levels (20, 40 and 80 μg) and were administered in 48 h intervals only in the absence of severe side-effects [11].

The unexpected long-term survival of 96 + months is noteworthy, and indicates the potential prolongation of life by the combination of chemotherapy and immunotherapy. In a pilot study of 19 patients who were treated with the same schedule for metastatic disease, we could demonstrate that patients who received total TrAb doses of more than 80 μg showed a trend towards both an improved median progression-free and overall survival (time to progression 21.9 versus 14.7 months, $P = 0.07$ log-rank; overall survival 47.2 versus 22.4 months, $P = 0.08$ log-rank) [11].

Further investigation in this field should restrict the strategy of HDCT, ASCT and immunotherapy to patients with hormone receptor-negative tumors with minimal residual disease, including maintenance therapy with monoclonal and/or trifunctional antibodies as well as biological modifiers. Controlled studies in this field are warranted.

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