ONKOLOGIE

Case Report · Kasuistik

Onkologie 2010;33:692–694
DOI: 10.1159/000322213

Published online: November 26, 2010

Stillbirth in Week 19 of Pregnancy Followed by Maternal Death as a Consequence of Refused Chemotherapy for Non-Hodgkin's Lymphoma – Significance of Adjuvant Chemotherapy in Women of Reproductive Age

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Keywords

Chemotherapy in pregnancy · Fertility preservation · Premature ovarian failure · Gastric non-Hodgkin's lymphoma · Cancer in pregnancy

Summary

Background: Due to rising cure rates in cancer, the question of preserving fertility in young female patients becomes more important. Especially in lymphomas, incidence and long-time survival have increased. Hematologists and gynecologists have to treat more and more female patients who wish to become pregnant despite their disease and/or after finishing treatment. **Case Report:** We report on a 28-year-old patient with highly malignant non-Hodgkin's lymphoma (peripheral T cell lymphoma, Ann Arbor stage IV) and main manifestation at the gastric antrum, with a distinct wish for becoming pregnant. Chemotherapy was strongly recommended to her, but she refused. After she had conceived, the disease recurred, followed by stillbirth in week 19 of gestation and death due to gastric perforation and septic shock. **Conclusions:** Facing the risk of sterility after chemotherapy should not induce patients to refuse chemotherapy and risk their lives. Treatment of young female cancer patients should therefore always include a thorough discussion about other ways of preserving fertility for the time after treatment. Such strategies exist, although their success is still limited and not every patient is eligible for them.

Schlüsselwörter

Chemotherapie, Schwangerschaft · Fertilitätserhalt · Vorzeitiges ovarielles Versagen · Non-Hodgkin-Lymphom, gastrisches · Krebs, Schwangerschaft

Zusammenfassung

Hintergrund: Aufgrund der ansteigenden Heilungsraten erhält die Frage des Fertilitätserhalts bei jungen Krebspatientinnen immer mehr Bedeutung. Besonders bei Lymphomen haben sowohl die Inzidenz als auch das Langzeitüberleben zugenommen. Hämatologen und Gynäko-Onkologen behandeln zunehmend Patientinnen, die während der Behandlung ihrer Erkrankung oder nach Abschluss der Behandlung einen Kinderwunsch haben. **Fallbericht:** Wir berichten über eine 28-jährige Patientin mit hochmalignem Non-Hodgkin-Lymphom des Magens (peripheres T-Zell-Lymphom, Ann Arbor-Stadium IV) und ausgeprägtem Kinderwunsch. Eine adjuvante Chemotherapie wurde ihr dringend empfohlen, sie lehnte jedoch ab. Nach Eintritt einer Schwangerschaft wurde ein Rezidiv des Lymphoms diagnostiziert. In der 19. Woche kam es zum Spätabort, wenig später starb die Patientin an gastrischer Perforation und septischem Schock. **Schlussfolgerungen:** Das Risiko einer sekundären Sterilität nach Abschluss einer Chemotherapie sollte Patientinnen nicht dazu verleiten, eine notwendige Chemotherapie abzulehnen und somit ihr eigenes Leben zu gefährden. Die Behandlung junger Krebspatientinnen sollte deshalb immer die Frage nach dem Fertilitätserhalt für die Zeit nach der Behandlung beinhalten. Möglichkeiten des Fertilitätserhalts für Krebspatientinnen existieren, auch wenn ihr Erfolg immer noch limitiert ist und nicht jede Patientin für eine der Methoden infrage kommt.

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Introduction

Due to increased cure rates in lymphomas, the question of preserving fertility in female patients becomes increasingly important. The incidence of lymphomas is generally on the rise in the population of Western industrialized countries. The incidence of non-Hodgkin's lymphoma in female patients has increased by over 70% during the last 25 years, for still unknown reasons. Chances of long-term survival have also increased over time: According to the figures of the Munich Tumor Registry, the 10-year overall survival for patients with Hodgkin's disease today is 71%, compared to 42% of 10-year survivors with non-Hodgkin's lymphoma [1]. In the USA, the 5-year overall survival for patients with non-Hodgkin's lymphoma increased from 58% in 1975–1979 to 82% in 1995–2000 [2].

Survival rates are expected to rise further, due to better treatment options with aggressive radio- and chemotherapy schemes. However, survival of lymphoma treatment is often linked with failure of gonadal function and infertility. More than 4500 women are newly diagnosed with non-Hodgkin's lymphoma in Germany per year, about 600 with Hodgkin's disease. About 10% of these patients are younger than 35 years and still in their reproductive age. If such patients do not receive appropriate counseling, there is the danger of their refusing treatment – with potentially fatal consequences like early recurrence of the disease and/or death. Here, we report on a 28-year-old patient suffering from a highly malignant non-Hodgkin's lymphoma (peripheral T-cell lymphoma) with main manifestation at the gastric antrum, with a distinct wish for becoming pregnant.

Case Report

The patient, a 28-year-old, apparently healthy woman of Italian origin, presented with stomach ache, fever, weight loss, and night sweats. The stomach ache was resistant to antibiotic therapy. A biopsy taken at a gastroscopy revealed multiple ulcers. The pathological exam showed a highly malignant non-Hodgkin's lymphoma of the peripheral T cell type, with main manifestation at the gastric antrum, Ann Arbor stage IV (fig. 1).

The patient underwent subtotal gastrectomy modified after Billroth II 2 months later. After surgery, she refused adjuvant chemotherapy according to the CHOP regimen (cyclophosphamide, adriamycin, vincristine, prednisone), suggested by 2 different oncologists. The reason for refusal was her urgent wish to become pregnant.

3 months after surgery, the patient conceived. 8 months after surgery, in week 19 of gestation, she presented with an acute abdomen. Clinical exams revealed gastric perforation with peritonitis in 4 quadrants, caused by recurrence of the T-cell lymphoma. Before surgery, fetal ultrasound was performed. It showed positive cardial action, regular biometry (biparietal diameter 40.9 mm, head circumference 146 mm, abdominal transversal diameter 44 mm, femur length 26.9 mm) and a polyhydramnion. Doppler of the umbilical artery showed a resistance index of 0.80. Cervical ultrasound showed a length of 18 mm without funneling. The fetus showed no abnormalities.

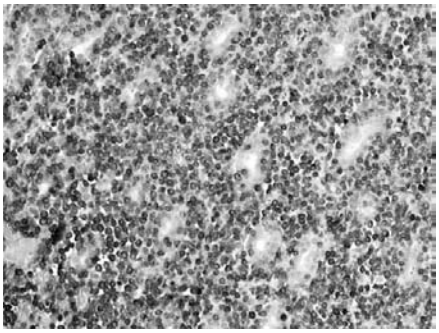

Fig. 1. Immunohistochemistry: Cells positive for CD3 (T cell marker) (Department of Pathology, Technical University of Munich).

A total resection of the remaining stomach and resection of duodenum and jejunum were performed. 3 days after surgery, stillbirth was diagnosed, followed by induced abortion. 2 weeks later, the patient developed wound rupture with a burst abdomen and became increasingly septic (rectal temperature: 39.1 °C, Quick 50% (international normalized ratio (INR) 1.5); activated partial thromboplastin time (aPTT) 64 s, leucocytes 14.44 G/l, thrombocytes 37 G/l, hemoglobin 11.7 g/dl; peritoneal swab: positive for *Klebsiella pneumoniae* and *Enterococcus faecium*). During re-laparatomy, the patient developed disseminated intravascular coagulation, although 12 red blood cell concentrates, 12 fresh-frozen plasma concentrates, and 2 thrombocyte concentrates had been transfused while she was undergoing surgery (Quick 49% (INR 1.5), aPTT 66 s, fibrinogen 145 mg/dl, antithrombin III (ATIII) 46%, leucocytes 4.58 G/dl, thrombocytes 28 G/l, hemoglobin 10 g/dl). Despite maximum therapy efforts, including packing and another re-laparatomy, the patient died of sepsis 2 days later. A following autopsy revealed infiltrates of the T cell lymphoma in the left adnex and the spleen.

Discussion

Long-term survival rates of young cancer patients are on the rise, but one major side effect of modern treatments is ovarian failure with subsequent infertility [3]. By reporting this case, we want to emphasize the need of expert counseling for women who have to undergo chemotherapy for a malignant disease and who wish to become pregnant and/or preserve fertility. For proper counseling of these patients, close interdisciplinary collaboration of specialists – hemato-oncology, gynecology, reproductive medicine, and psychotherapy – is warranted.

Ovarian damage and failure is a common side effect of curative chemotherapy. Damage done to the ovaries by chemotherapeutic agents is dependent on the regimen and dose applied as well as on the age of the patient. Older women have a higher incidence of complete ovarian failure and permanent infertility, compared to younger women [4]. Meirow et al. [5] examined a collective of 168 female cancer patients with a mean age of 29.9 years and proved normal ovarian function prior to treatment. All patients had undergone conventional chemotherapy regimens for 4 types of cancer (acute myeloic leucemia (47), breast cancer (38), Hodgkin's disease (47), non-Hodgkin's lymphoma (36)). They found an overall

rate of primary ovarian failure (POF) of 34%. Alkylating agents were found to impose the highest risk of causing ovarian failure (commonly used alkylating agents are, e.g., cyclophosphamide, chlorambucil, procarbazine, busulfan or carmustin) [3]. The CHOP regimen that was suggested to our patient contains cyclophosphamide, which is especially harmful to ovarian function, as animal studies have shown [6].

A French study by Franchi-Rezgui et al. [7] reports on 84 women of fertile age (average 27.4 years) with either Hodgkin's or non-Hodgkin's lymphoma who had received chemotherapy with alkylating agents. After an observation time of 100 months, 31 women had conceived. 34 women showed primary ovarian failure. 19 women had kept relative fertility. Of 16 women with recurrent disease treated by high-dose chemotherapy, 3 became pregnant.

However, POF does not occur in every patient: About one-third of the patients with non-Hodgkin's lymphoma will experience a recurrence of normal menstrual cycles after finishing chemotherapy [5, 7]. Facing the risk of sterility after chemotherapy should not induce patients to refuse chemotherapy and endanger their lives – as our patient did. Treatment of young female cancer patients should always include a discussion on possible ways of preserving fertility for the time after treatment. German university centers for reproductive medicine have recently published a concept paper about fertility preservation for patients at risk of POF after chemotherapy [8]. Possible strategies mentioned are:

- surgical methods for preserving internal reproductive organs affected by a tumor or for protecting them from radiation damage [9, 10],
- protection of ovaries by suppressing gonadal function with gonadotropin-releasing hormone (GnRH) agonists ([11–13], *www.clinicaltrials.gov* (Italian study Promises Gym6), *www.germanbreastgroup.de* (German study ZORO)),
- cryoconservation of embryos after in vitro fertilization [14],
- cryoconservation of oocytes [13, 15],
- cryoconservation of ovarian tissue with re-implantation after treatment [16, 17].

All of these strategies are not part of today's clinical routine – multiple studies exist that have demonstrated them to be successful, but further evidence in prospective studies has to be collected.

Our case shows the importance of explaining to the patients several strategies that are currently available. At the same time, honest communication has to be maintained [11, 18]. The patient should know about the risk of ovarian failure as well as about the limited access to and success of the fertility preservation methods available today.

Conflict of Interest

None of the authors has received any financial support or benefit from commercial sources or has other financial interests that might create a potential conflict of interest.

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