PREGNANCY IN A PATIENT RECEIVING BUSULPHAN FOR CHRONIC MYELOID LEUKAEMIA

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ABSTRACT

A 33-year-old Malay lady with chronic myeloid leukaemia (CML) became amenorrhoeic during therapy with busulphan. Pregnancy was diagnosed via a urine pregnancy test and an ultrasound confirmed a viable foetus at 16 weeks. The busulphan was stopped. Her pregnancy was unremarkable and continued till term. She delivered a healthy child.

Keywords: *busulphan, chronic myeloid leukaemia (CML), pregnancy, amenorrhoea.*

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INTRODUCTION

Busulphan is a sulphonic acid ester (1-4, dimethanesulfonoxybutane) which is an orally absorbed alkylating agent. It is widely used in the therapy of CML because its cytotoxic activity results in primary damage or destruction of haematopoietic cells. It is highly effective when administered either as maintenance therapy or intermittently as required. Toxicity, however, has remained extremely low, the only serious effect noted has been bone marrow depression, and even this is very unusual if the dosage is kept within prescribed limits. Other side effects of busulphan are few. The most common are skin pigmentation and amenorrhoea. More serious is a syndrome with features resembling Addison's disease (characterised by weight loss, severe weakness, fatigue, anorexia, nausea and pigmentation). Interstitial pulmonary fibrosis can also occur.

Busulphan appears to have a profound effect on gonadal tissue. It is known to cause sterility resulting from amenorrhoea and testicular atrophy[1]. Busulphan also has a teratogenic effect[2]. We report a patient who conceived while on busulphan therapy, and the pregnancy was uneventful with the delivery of a healthy male baby.

CASE REPORT

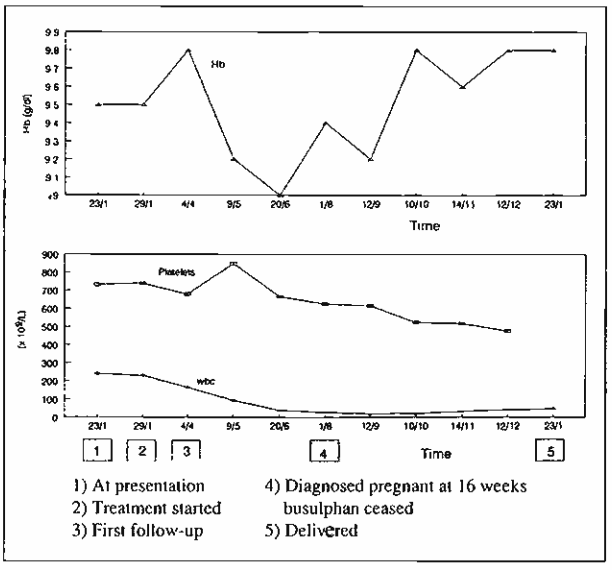
SM was a 39-year-old Malay lady. She presented in late December 1990 with complaints of left hypochondrium discomfort and swelling. She had just delivered her fifth child three months earlier. She was otherwise healthy. She did not receive any medication.

She was neither pale nor jaundiced. There was no lymphadenopathy or evidence of bleeding tendencies. There was splenomegaly 11 cm below the left costal margin and hepatomegaly of 3 cm below the right costal margin. The rest of the physical examination was normal.

The diagnosis of chronic myeloid leukaemia was based on hepatosplenomegaly, leukocytosis of 239 x 10^9/L, thrombocytosis of 732 x 10^9/L and characteristic bone marrow aspirate findings which were consistent with CML, with a low neutrophil alkaline phosphatase score of 14/100 neutrophils.

Treatment with busulphan 4mg daily and allopurinol 100mg t.d.s. was begun on 29th January 1991. She was discharged well on 8th February 1991. She was well on her first follow-up ie about eight weeks after discharge, with a total white count of 165 x 10^9/L and platelet of 680 x 10^9/L. During her second visit on 1st August 1991, ie after about seven months of treatment, she complained of amenorrhoea of three months duration, her last menstrual period being on 9th May 1991. A urine pregnancy test done was positive and she was referred to the gynaecology unit for further management. An ultrasound confirmed a 16-week-old normal viable foetus. Busulphan was immediately stopped. She subsequently did not require any treatment throughout her pregnancy as her total white counts ranged from 44.7 x 10^9/L to 92 x 10^9/L. The pregnancy was uneventful and she delivered via a Caesarean section due to an oblique lie on 23rd January 1992. It was a normal full term male infant weighing 2.02 kg, with an Apgar score of 7. Fig 1 shows the progress of the patient.

Fig 1 – Progress of the patient



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DISCUSSION

The problem of the use of chemotherapeutic agents during pregnancy is not uncommon[1]. This report documents the occurrence of pregnancy during therapy with busulphan in a young patient with CML. Altogether, this patient had received a total dose of 688mg of busulphan.

Busulphan has been shown to cause ovarian failure two to three months after commencing therapy. There are reports stating the development of amenorrhoea with busulphan, the first report was published in 1956[3]. Galton observed the occurrence of permanent amenorrhoea in all four premenopausal patients[4]. Other similar observations were noted by Ghose and Chartterjae[5], Belohorsky and his workers[6]. In the study[6], 10 premenopausal women became amenorrhoeic, 2 were examined post-mortem and atrophy of both ovaries and endometrium with intact pituitary glands were noted. One patient developed atrophic changes in the vagina, leading to severe dyspareunia requiring oestrogen therapy. Kennis and workers described a male who developed testicular atrophy[7].

Despite the above findings, Oded Shalev and workers[8] reported resolution of ovarian failure with the development of pregnancy almost simultaneously with CML relapse. In this report, however, the patient became pregnant when she was showing haematological response to treatment (total white count: from 239 x 10^9/L to 92 x 10^9/L).

Moloney[9] observed that 12 patients with CML on busulphan were pregnant. All except one delivered a normal healthy infant. The single infant[10] had ovarian atrophy in addition to multiple other defects. Her mother had also received 6-mercaptopurine and radiation in addition to busulphan during the early pregnancy. Studies done by Pelloux and workers[11] showed that busulphan treatment produced a significant reduction in the number of oocytes and in ovarian weight and volume of the rat progeny. The drug appeared to have a selective action on the primary oocyte or spermatocyte, other cellular structures were unaltered. It was noted that with the exception of the lack of primary gonadocytes, the infant rats were perfectly normal.

In this report, the good health of the infant indicates that busulphan had no apparent teratogenic effect, even though it was inadvertently taken during the first trimester of pregnancy. If at all busulphan causes severe teratogenicity, the mother would have had a spontaneous abortion. However, more studies or long term follow-up should be done in order to determine the late side effects of busulphan on the infant when he grows up.

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