CASE REPORT

Leukemia and Pregnancy: Observation of a Case Treated with Busulfan (Myleran)

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While the effects of cancer chemotherapy on the embryonic laboratory animal have been extensively studied and documented, a review of the literature reveals a paucity of comparable information regarding clinical cases. Relative to busulfan (Myleran) therapy in particular, we found only four cases reported. Of these, three patients with chronic myelocytic leukemia, treated with busulfan alone, bore normal infants which apparently have continued to develop normally over the years. In one of these cases, the drug had been in use at conception and was continued throughout gestation. In another, busulfan was administered during the second and third month of pregnancy. The fourth case, treated alternately with x-radiation, 6-mercaptopurine and busulfan, bore a malformed infant which died at two months.

This report presents our experience in the case of a young woman who (1) conceived while receiving therapeutic doses of busulfan; (2) carried the pregnancy to normal term despite continued chemotherapy during the first months of gestation; and (3) delivered a normal male infant.

Clinical history of patient: A.T., 28 years of age. Five normal pregnancies, and one abortion which had occurred three years before our examination of the patient. There was no history of serious illness prior to the abortion, which had been accompanied by hemorrhage. In the year following the abortion, the patient complained of increasing asthenia, fatigue, anorexia, and dyspnea on moderate effort. These symptoms gradually increased in severity, with added complaints of diffuse pain in the posterior thoracic region, sudden and intense in onset; a sensation of heaviness in the upper left quadrant of the abdomen and epigastric region; constipation, blurred vision and weight loss.

Physical examination: A pale young woman, weight 42 Kg.; height 1.57 M.; pulse 100/min.; blood pressure 90/50; temperature 36.5 C. Abdominal examination disclosed hepatomegaly grade I; splenomegaly grade IV, slightly painful on palpation.

Laboratory examination: Urinalysis: normal. Blood serology: normal. Hematologic studies: hemoglobin 11.0 Gm. per 100 cc.; hematocrit 35 per cent; leukocytes 196,000 per mm.³; lymphocytes 3 per cent; monocytes 1 per cent; basophils 5 per cent; eosinophils 2 per cent; neutrophils 89 per cent; myeloblasts 1.5 per cent; promyelocytes 5 per cent; myelocytes 20.5 per cent; metamyelocytes 17 per cent; band neutrophils 13 per cent; segmented neutrophils 32 per cent. Bone marrow: hypercromia (XXX); erythro/granulopoiesis ratio: 1 to 23; ratio of immature to adult cells: 7.4 to 1; megakaryocytes 4.6. Diagnosis: Chronic myelocytic leukemia.

Treatment: Chemotherapy was instituted with busulfan as follows:

4 mg. daily—Sept. 6–Oct. 3, 1958
6 mg. daily—Oct. 4–Nov. 12
2 mg. daily—Nov. 13–Nov. 21

At this point, therapy was temporarily discontinued. It was evident that the patient had
become pregnant. The last menstrual period had begun on September 29 (23 days after the start of chemotherapy). Omission of the next period was not considered significant, as busulfan has been known to induce amenorrhea. Subsequently, we estimated the date of conception at approximately October 11, 14 days after the last menstruation.

A good remission was obtained in this initial course of busulfan therapy, with marked reduction of splenomegaly in six weeks. The patient's general condition was much improved, as evidenced by disappearance of the sensation of abdominal heaviness, asthenia, fatigue and dyspnea. Except for a moderate anemia, laboratory studies were normal at the time therapy was suspended.

The patient continued in good remission throughout a normal pregnancy and was delivered of a normal male infant on July 1, 1959. On follow-up, the mother remained in apparently good health, except for moderate anemia until the end of the year. Thereafter, increasing asthenia was observed. Laboratory tests showed elevation of the leukocyte count with reappearance of immature granulocytic cells.

On February 10, 1960, therapy was reinstated along the following lines:
- 500 cc. blood transfusion—Feb. 10 and 18
- 4 mg. busulfan daily—Feb. 11-27
- 2 mg. busulfan daily—March 5-10
- 500 cc. blood transfusion—March 13 and 24

Hematologic data are given in the accompanying chart (fig. 1). The patient responded to therapy with a second good remission.

Clinical history of the child: Physical examination at birth showed a normal male infant. Weight 2.300 Kg.; height 46.5 cm.; cephalic perimeter 32 cm.; thoracic perimeter 29.5. The infant had two inferior medial incisors. Laboratory studies of blood from the umbilical cord gave the following results: erythrocytes 6,800,000 per mm. 3; hemoglobin 20.0 Gm. per 100 cc.; hematocrit 64 per cent; leukocytes 10,750; normoblasts 72 per cent; polychromatophilia (XXX).

The infant was placed on an artificial diet and gained weight gradually. Hematologic
findings during the first three weeks of life continued normal. In the fourth week, fever, diarrhea and anorexia developed. Under treatment with antibiotics and fluids, the child rallied for a few days, then relapsed and died 30 days after birth.

Histopathologic data: Autopsy was incomplete as study of the cranial cavity was not permitted. Physical examination showed a slightly underdeveloped male infant, essentially normal; the testicles were in the scrotum and were histologically normal. Placenta: normal. Passive congestion existed in all organs. Intestines were essentially normal. Liver: slightly enlarged with an anomalous deviation of the left lobe; microscopically, a diffuse pericentral fatty degeneration was observed. Spleen: bilobar; in this organ as well as the thymus and some lymph nodes there was hypoplasia of lymphoid tissue. Adrenals: atrophic (1.4 Gm. each), with some hypolipoidization. Lungs: foci of atelectasis. Microscopically, macrophages were observed in the septa and alveoli. Neither inclusion bodies nor cytomegaly were found. The ductus arteriosus was in the process of occlusion. Blood cultures from the right cardiac cavities revealed micrococcus (Staphylococcus) pyogenes, coagulase-positive. Cause of death: acute staphylococcus infection.

DISCUSSION

Laboratory studies have shown that in the pregnant rat, chemotherapeutic agents can pass the placental barrier and cause abortion, resorption, or teratogenesis of the fetus. In one such study, Murphy and associates demonstrated that a single LD₅₀ intraperitoneal injection of busulfan proved teratogenic to the rat embryo, although less so than the other four drugs studied. (Interestingly, the lesser toxicity of busulfan was attributed to its low solubility and the possibility that it may penetrate the placenta slowly and in insufficient concentration to effect acute changes.)

While experimental laboratory studies generally serve as a clinical guide, we are inclined to agree with Sokal and Wagner that such data may not be directly applicable to the human patient. Particularly in consideration of the major differences in the human and rodent gestational period and time cycle of fetal development, the dosage, route of administration, and metabolism of the drug in the presence or absence of a disease process are all important.

Diamond et al. cite the case of a pregnant woman, treated alternately with x-radiation, 6-mercaptopurine and busulfan, who subsequently gave birth to a malformed infant. While conceding that the anomalies noted in the infant are common as spontaneous, idiopathic occurrences, they attribute the abnormalities in this case solely to the use of busulfan. We would take exception to this conclusion, since therapy with either 6-mercaptopurine or busulfan alone has been shown to permit normal development of the human fetus. It would seem more likely, if the deviations were not spontaneous, that they resulted from a synergistic or additive toxicity of the three therapeutic agents employed.

In the present case, conception occurred despite therapeutic dosage with busulfan, which is known to induce amenorrhea, endometrial hypoplasia and gonadal atrophy. Since cessation of the menses was considered to be simply a side effect of the drug, busulfan therapy was continued through the first few months of pregnancy. Theoretically, this should have resulted in abortion or malformation of the fetus. However, gestation ran an uncomplicated course with normal delivery of an infant which was found to be
normal on physical examination and laboratory tests. In view of the foregoing, the few minor and commonplace anomalies disclosed at autopsy cannot reasonably be attributed to busulfan.

Our own experience, and that of others, would seem to indicate that the use of a single chemotherapeutic agent during pregnancy may not be as hazardous to the fetus as previously thought. In view of the individual variables inherent in each patient and the few recorded case histories, however, it would be impossible to offer any recommendations on such treatment. As Bierman and Sokal have pointed out, a sound guide for management of this problem would depend on analysis of a large series of reported cases, with long-term follow-up information on children born under such circumstances.

We are in agreement with Bierman on the desirability of creating a center where the development of such children could be under continuous observation and study, thus permitting accumulation of the much-needed clinical and statistical information.

**Summary**

The case of a 28 year old woman with chronic myelocytic leukemia, who conceived while under treatment with busulfan, is reported.

Pregnancy, delivery, and the infant were normal. The child died one month later of a Staphylococcus infection. Autopsy disclosed a few minor and commonplace anomalies which the authors believe cannot reasonably be attributed to busulfan.

A review of the literature on pregnancy and leukemia is cited.

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