Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy

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Background: The use of anthracyclines in patients with cancer has been associated with the presence, even when standard doses were employed, of cardiac toxicity, most frequently after 5 years of therapy. Treatment of cancer during pregnancy remains a dilemma because cytotoxic therapy has been associated with the presence of severe side-effects. The outcome of children that received anthracyclines during pregnancy, including during the first trimester, remain unknown because long-term follow-up is not available.

Patients and methods: Eighty-one children whose mothers (29 acute leukemia, 33 malignant lymphoma and 19 Hodgkin’s disease) were treated with cytotoxic drugs, including anthracyclines, during pregnancy were evaluated to detect cardiac toxicity, including clinical evaluation and echocardiogram [all parameters were evaluated, but fraction shortening (FS) was taking as the best parameter to evaluate cardiac toxicity in children] every 5 years after birth until 29 years of age.

Results: Children with actual age of 9.3–29.5 years (mean 17.1) did not show any clinical date of cardiac disfunction, in all cases echocardiogram was normal and FS did not showed any abnormality during the follow-up.

Conclusions: The use of anthracyclines did not show any clinical or echocardiogram evidence of late cardiac toxicity. We hope that the present report increases the number of reports of the long-term follow-up of children who received cytotoxic drugs, in order to define the best treatment in this special patient setting.

Key words: acute leukemia, cardiac toxicity, Hodgkin’s disease, malignant lymphoma, pregnancy: complicated

Introduction

Cancer remains a leading cause of death in women of childbearing age, but the association of pregnancy and cancer appear to be uncommon, probably because most cases have not been reported or because the rate of early fetal loss (spontaneous or induced) could be higher in these women. Treatment of cancer during pregnancy remains a dilemma, because cytotoxic therapy has been associated with increased frequency of congenital malformations; however, the presence of severe congenital malformations have recently been considered to occur in <1% of all cases [1, 2]. Treatment of patients with some hematological malignancies, including acute leukemia, Hodgkin’s disease and malignant lymphoma, has been considered, which will be treated with curative intent. However, late toxicities have not been reported in children that received aggressive chemotherapy during pregnancy, and outcomes remain unknown. Some years ago, we reported the clinical outcome in 84 children who received chemotherapy in utero, including 58 cases during the first trimester, with no evidence of clinical malformations. Growth and development were normal, as were neurological, psychological and educational performance, without evidence of abnormalities in learning and behavior. Cytogenetic studies were normal and no cancer or acute leukemia has been observed [3].

A major concern for these children and their physicians is the possibility of late heart disease as a consequence of exposure to an anthracycline during pregnancy. Moreover, anthracyclines can cross the placenta and fetal tissues showed high levels of anthracyclines metabolites [11, 12]. Thus, the possibility of late cardiac damage in these children will be considered. To assess these possibilities we began a surveillance study in 1983, the end point of which was to evaluate the presence of cardiac toxicity in children treated with aggressive chemotherapy, including anthracyclines during pregnancy. Although, myocardial biopsy is the best way to detect cardiac toxicity, the use of an invasive method in apparently healthy children was not considered appropriate. Thus, echocardiogram was eligible for use in this study, because it is the most feasible non-invasive tool to assess function studies in follow-up studies [10, 13, 14], especially in children who have received anthracyclines [15–19].

Patients and methods

All children >5 years old who received anthracyclines during pregnancy were considered candidates for this study. In all cases, echocardiogram was
performed, and evaluation including left ventricular internal dimension, septal wall thickness and posterior wall thickness were measured in end-diastole, which is defined as the onset of the QRS complex, and in end-systole, which is defined as the first high-frequency signal of the second heart sound on the phonocardiogram. Carotid pulse tracing was used to measure left ventricular ejection time and to estimate end-systolic pressure.

Left ventricular end-diastolic and end-systolic dimensions, fractional shortening (FS), were measured by two cardiologists who did not know the reason for the study. Taking into consideration that FS has been recommended as the best method to evaluate late cardiac toxicity in patients with cancer and who received anthracyclines [6, 8, 10], we selected these results to define the presence of cardiac damage: a value of <28% was considered as the cut-off level to define the presence of cardiac toxicity. An echocardiogram was performed at 5 years old as baseline (some children were >5 years when the study began); if the echocardiogram was normal, we repeated the study every 5 years until the age of 20 years or last follow-up. If the echocardiogram showed some alteration, FS < 28%, the study was repeated 30 days later; additional studies were performed if clinically indicated. Clinical cardiac evaluation was performed every 6 months during the first 5 years of life by a cardiologist that did not known the patient. If the children remained asymptomatic, clinical evaluation were performed every year. X-ray studies were performed only if clinical signs or symptoms were observed.

The study was approved by the ethics committee of our institution (protocol 1983-016HO), and parents or legal representatives signed an informed consent form to participate in the study.

Taking into consideration the uniform population, no statistical analysis was performed to define prognostic factors.

results

Eighty-one children were included in the present report. Table 1 shows the clinical characteristics, type and dose of anthracyclines and number of echocardiograms.

<table>
<thead>
<tr>
<th>Number</th>
<th>Acute leukemia</th>
<th>Lymphoma</th>
<th>Hodgkin’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>36.4</td>
<td>33–39</td>
<td>33.9</td>
</tr>
<tr>
<td>Last</td>
<td>35.2</td>
<td>34–38</td>
<td>34.5</td>
</tr>
</tbody>
</table>

No clinical evidence of cardiac disease has been observed until now and no further studies were necessary in all children. In all cases all the parameters evaluated by the echocardiogram were normal, and FS was normal in the baseline study and in all studies performed. Intraindividual changes during follow-up remained inside normal values (Table 2).

discussion

Cardiac toxicity secondary to anthracyclines has been extensively documented [1–8] and multiple studies have been designed to monitor the presence of early findings to prevent or ameliorate congestive heart failure [10–14]. Most of these studies showed that age, cumulative dose and use of radiation therapy to chest increase the possibility of cardiac damage in children and adults. Treatment of cancer patients during pregnancy is very difficult because most of the drugs employed for treatment cross the placenta and eventually can produce congenital malformations; however, some reports have indicated that the presence of congenital malformations will be low, and in most cases is not lethal [3].

Presence of late events is very rare, but most reports only included delivery and the first months or years (<5 years) of follow-up, and in some instances late effects were not considered. When we began the present study, it was not known whether children that received anthracyclines during pregnancy could develop late toxicity, and in the present paper we considered that the end point. Our results showed that no clinical, laboratory or cytogenetic abnormalities were observed, and growth, development and learning were considered normal when compared with children that did not receive chemotherapy during pregnancy, even when cytotoxic therapy was administered during the first trimester.

In children with cancer and who were treated with anthracyclines at standard doses, the presence of congestive heart failure has been observed 5 years after receiving anthracyclines [5–7]. To our knowledge no studies about the safety of anthracycline administration during pregnancy considering the long-term effects on the fetus have been undertaken. It has been demonstrated that anthracyclines can cross the placenta and different concentrations of drugs have been demonstrated, but no tissue evidence of cardiac damage was mentioned [11]. Meyer-Wittpuff et al. [20] monitored a fetus during pregnancy when the mother received anthracycline-based chemotherapy and no alterations were observed; however, no longer follow-up was reported. Germann
et al. [12] reported an analysis of 160 children who received anthracyclines during pregnancy and reported three cases of cardiac toxicity, included two lethal cases, but no details were included. In the same report, different mechanisms were considered to explain the low number of toxicities secondary to anthracycline administration and the authors concluded that these drugs could be employed during pregnancy if standard doses are administered. Also, it appears that the pharmacokinetics of several drugs are different in children compared with adults [21], and one hypothesis is that the clearance during pregnancy is accelerated, and for this reason no chronic damage is evident in some tissues. On the other hand, our results confirm previous reports that the use of chemotherapy during pregnancy is feasible and safe if the attempt is curative, with the use of standard doses and schedules similar to non-pregnant patients, even when the drugs are employed during the first trimester. The present paper presents the first evidence based on a longer follow-up employing adequate clinical and echocardiogram evaluation that can demonstrate that the use of anthracyclines during pregnancy is not associated with cardiac damage, even at 20 years of follow-up. It is evident that we cannot provide definitive conclusions, because although the number of patients was large, it does not reflect the total number of cases, and the study was undertaken in a single center. We conclude that it is necessary for a multicentric, probably retrospective, analysis to be undertaken in a single center. We hope that physicians who treat patients with cancer during pregnancy report their results in order to help to define the best treatment in these patients, and to have more information about the presence of late toxicities associated with cancer treatment during pregnancy.

**references**