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Research Article

Pregnancy and Hematological Malignancies - Can Improve Outcome

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Abstract

The treatment of cancer during pregnancy, has been changed in the last years, actually is acceptable the use the standard chemotherapy regimens, even in first trimester, and late toxicities has not been reported, however, the role of pregnancy in the outcome of hematological malignancies (HM) has not been reported. Thus we review our experience in a large number of cases and longer follow-up in mother HM, to assess if pregnancy influence the outcome on HM. Retrospectively we reviewed the cases of patients with pathological diagnosis of HM and pregnant that received chemotherapy during pregnancy and they were matched with non-pregnant patients, with same age, socio-economical and scholar conditions and HM who received the same chemotherapy, Outcome were measured with progression-free survival (PFS) and overall survival (OS). From 1975 to 2016, we recruit 202 pregnant patients with pathological diagnosis of HM, in whose no obstetrical complications were observed; delivery and post-partum was normal, late toxicities in mothers were minimal, when a new pregnancy was desired it was normal; chemotherapy administered during pregnancy was well tolerated, PFS and OS were statistically better in pregnant patients when compared with no pregnant women. Children did not have any congenital malformations, preterm and low-weight was minimal, and did no influence development. All clinical, laboratory, neurocognitive evaluations and echocardiogram were normal, compared with a control group of the same age, economic, social and scholar degree. No acute leukemia or second neoplasm has been observed in mothers or newborns.

Conclusion: We show that pregnant mothers with HM, had a statistically differences in PFS and OS, compared with a matched group of non-pregnant patients. We did not have a scientific explication about it is a probably protective role of pregnancy in this setting of patients.

INTRODUCTION

Cancer occurs in approximately 1/1000 top 1/200 pregnancies; hematological malignancies (HM) occupy between the fifth to sixth place of frequency, the HM more frequent are acute leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma .associated to younger females, another HM are very infrequent [1,2]. Diagnosis of HM during pregnancy the use of some diagnostic studies and the use of chemotherapy and/or radiotherapy, remain to be considered dangerous to mothers and fetus, and are associated with excessive risks. Therefore, to the rarity of HM during pregnancy, most of the literature is based in retrospective, case reports, moreover, most studies included a low-number of cases, did not have a longer follow-up to detect late adverse events in mothers and newborns, and did not performed periodically evaluations; thus the better treatment remain to be defined [3-11]. Also, we did not found any report that analyzes the role on the outcome in this setting of patients.

In our institution we began an observational longitudinal study to evaluate if the use of conventional chemotherapy could be employed during pregnancy, even in first trimester, the end-points were: tolerance to hematological treatment, response and outcome, measured with progression-free survival (PFS) and overall survival (OS), obstetrical complications, periodically evaluation in both: mother and newborn, with special attention to late adverse events.

PATIENTS AND METHODS

From June 1975 to December 2016, we diagnosed and treated 202 cases of patients with HM and pregnancy, the median follow-up was 22.4 (range 3.8 to 40,8) years.

Mothers

They were diagnosed and treated, according with the criteria at the time of diagnosis, when pregnancy was documented, obstetrical evaluation was conducted by an expert obstetrician,

and they evaluated the obstetrical and nutritional condition and the status of the fetus. Laboratory and fetal ultrasound. Subsequently, the patients were evaluated every 2 weeks, until delivery. If any abnormalities were observed, quickly treatment was employed. All patients were evaluated by a nutritionist and received supplementary protein intake, vitamins and folic acid. Psychological support was administered every 4 weeks to mother and spouse. . Delivery was performed according to the obstetrical conditions; in most cases chemotherapy were stopped 2 to 3 weeks before delivery to avoid the risk of severe neutropenia or infection in newborns. Chemotherapy was administered at schedules and doses with the time of diagnosis, delayed, reduction of dose or stopping, was based in the hematological conditions. Progression-free survival (PFS) was considered from the date of complete response was achieved until relapse, death or last follow-up; overall survival (OS) was considered from the time of diagnosis to the date of death from any cause). If relapse, they were treated according to the treatment indicated. If the patient gets pregnant again, she was attended in the same hospital center. If the patient developed any toxicity that was considered secondary to treatment, it was indicated. Radiotherapy was administered after 3 or 4 weeks after delivery, in patients with clinical indicated [12].

Mothers in this group were matched in proportion 1:1, with non-pregnant patients with the same HM, that were treated at the same time (≥ 3 months), chemotherapy employed, age, socio-economical status and scholar degree, to evaluate acute and late adverse events and outcome. The Cox proportional -hazard regression method was sued to fit univariate and multivariate survival models for PFS and OS. The outcome of interest was reported as hazard ratio (HR) with 95% Confidence Interval (CI) or progression or death from any cause. P-values < 0.05 were considered significant.

Children

At birth, newborns were carefully examined for a neonatologist to detect any congenital malformations. Height and weight were recorded. Complete blood counts and serum chemistry were performed. Subsequently, children were carefully evaluated at the age of 3, 6, 12, 18 and 24, 36 and 48 months, subsequently, until 20 years, annually. If any clinical condition was observed, studies were performed according to the clinical dates. Those children were matched with a group that were healthy children of the same age, sex, socio-economic status, and scholar degree in proportion 1:1. At each visit, physical examination was conducted; laboratory tests were complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase and beta 2 microglobuline. Biometric data were obtained and compared to normal standard of clinical development in Mexican children [13,14]. Psychologist conducted a panel of Intelligence tests according to the age to evaluate verbal intelligence, velocity of processing memory, verbal working, alertness, attention, and the process to manage environment problems used the Wechsler Intelligence Scale for Children [15], the control group was employed in children with 6 years. Neurological evaluation was performed by neurologists that did not know the status of the children. Cardiac function was performed with echocardiogram, until 30 years old, that is a reasonable date to associated the possibility of cardiac damage employed in chemotherapy; that include left ventricular interval dimension, septal wall thickness and posterior wall, thickness and posterior well ; thickness measured in end-diastolic which is defined at the first high-frequency signal of the second heart sound on the phonocardiogram; carotid pulse tracking was used to measure left-ventricular ejection time and to estimate end systolic pressure, left ventricular end diastolic and end systolic dimension, fractional shortening (FS) were measured by two cardiologist. Taking in consideration that FS has been recommended as the best method to evaluate late cardiac toxicity in patients with cancer that received anthracyclines, we select that results to define the presence of cardiac damage a level of FS < 28% was considered the cut-off level to define the presence of cardiac toxicity. If the children show a level < 28% without any clinical evidence of cardiac advance, they watch-over and repeat the study a 3 months, if normal, we considered the study as false-positive, but, if the children show any clinical abnormality, additional studies were performed [16,17]. A social worker visit the teacher of all children and the end of any school year, to evaluate the capacity of learning, sociality with other children, the school attendance, scholar qualifications. The same social worker visit every year the home, and interview the parents, brothers, and friend, to evaluate if the children show any abnormality with friendships, or family. Our institution has access to the electronic file of all patients attended, thus we can detect if the children show any disease, the treatment and evolution. When these children have age to parenthood, we investigate if those children show any abnormalities: some of those children married and had children.

RESULTS

Table 1-3 shows the clinical characteristics, histology, stage, treatments, response, obstetrical and fetal complications, status of newborns; and outcome in mothers and newborns. No statistically differences were observed between pregnant and no pregnant patients in relationship to tolerance to chemotherapy adverse events: nausea, vomiting, alopecia, neurological and hematological events compared with matched patients in the three groups. Granulocytopenia grades III and IV were observed in 12 % of cycles of chemotherapy in patients with acute leukemia, no different to 10% in non-pregnant women. Delay in treatment was between 4 to 11 (median 7.2) days in pregnant and 3 to 15 (median 6.9) days in patients with acute leukemia. Patients with Hodgkin lymphoma and diffuse large B-cell lymphoma did not present grade III or IV granulocytopenia. Granulocytopenia grade I or II in patients with acute leukemia were 20%, no different to no pregnant patients (23%). Delays in treatment were minimal in Hodgkin lymphoma and diffuse large B-cell lymphoma: 7% and 9% respectively. Severe infection were not observed, delivery was planned to be administered at least 3 weeks before the last chemotherapy, to avoid the risk of severe granulocytopenia or infections, chemotherapy was restarted 10 to 14 days after delivery [18]. At the time of delivery, pregnant and no-pregnant patients had a normal nutritional status. Anti-emetic drugs and colony stimulating factors were employed based in clinical condition. Neither obstetrical complication was observed. Delivery was vaginal in most cases, and no post-delivery complications were observed. Complete response was similar in pregnant and non-pregnant patients but, actuarial

Table 1: Acute leukemia.

	No%		
	Pregnant	**No-Pregnant**	**p**
Cases	46 (100)	51 (100)	
Age(years) range	21 - 38	25- 36	0.666
Median	28.4	29.9	0.801
First pregnancy	22 (42.826)		
First trimester	14 (30.498)		
Histology			
Myeloblastic	30 (65.200)	29 (56.823)	0.445
Lymphoblastic	16 (34.670)	22 (43.133)	0.201
Chemotherapy			
CVPD	6(13.00)	9 (17.611)	0.666
Ara C/Anthracycline	40 (86.956)	42 (82.334)	0.886
Complete response	40 (86.918)	42 (82.301)	0.776
Obstetrical complications	0		
Fetal complications	0		
Vaginal delivery	33(71.709)		
Ovarian failure	1(2.122)	0	
Parenthood	8(13.002)	6 (11.745)	0.301
Two patients had two pregnancies			
Outcome			
PFS*	66%(95%CI:59% - 73%)	56% (95%CI:50%-63%)	< 0.010
OS**	71(95%CI:64%-80%)	64%(95%CI:58%-72%)	< 0.010
Children			
Preterm (<36 weeks	3 (6.5)		
Low-weight (< 2500 g	5 (8.6)		
Congenital malformations	0		

Abbreviations: CVPD: Cyclophosphamide, Vincristine, Prednisone and Anthracycline (Daunorubicin or doxorubicin)
*At 10 Actuarial curves at 10 years, progression-free survival, OS: overall survival.

Table 2: Hodgkin lymphoma.

	No (%)		
	Pregnant	**No-pregnant**	**p**
Cases	98 (100%)	105 (100)	
Age (years) median	22.8	23.9	0.566
Range	20.0-27.3	21.2-28.6	
First pregnancy	46 (46.912		
First trimester	28 (28.554		
Stage			
I -II	44 (44.867)	48 (45.734)	0.856
III-IV	54(55.198)	58 (55.202)	0.854
Histology			
Nodular sclerosis	65 (66.356)	77 (73.389)	0.112
Depletion lymphocytic	30(30.623)	28 (26.655)	0.201
Not classified	2 (2.00)	0	
Treatment			
MOPP	5 (5.123)	5 (4.756)	0.555
MOPP/ABVD	3 (3.0)	0	
ABVD	90 (91.801)	100 (95.259)	0.745
Complete response	92 (93.823)	97 (92.322)	0.505
Obstetrical complications	0		
Fetal complications	0		
Ovarian failure	0		
Vaginal delivery	89 (90.888)		
Outcome			

PFS *	89% (95%CI:83%-97%)	72%(95%CI:64%-81%)	< 0.01
OS**	92%(95%CI:86-97%)	81%(95%CI:70%-93%)	< 0.01
Children			
Preterm	2(2.002)		
Low-weight (<2500 g)	4 (4.082)		
Congenital malformations	0		

Abbreviations: MOPP (Mustard Nitrogen, Vincristine, Procarbazine, Prednisone); MOPP/ABVD (MOPP + ABVD; adriamycine, bleomycin, vinblastine and dacarbazine), CI: Confidence Interval, PFS; Progression-Free Survival; OS: Overall Survival

Table 3: Non-Hodgkin lymphoma.

	No%		
	Pregnant	**Non-Pregnant**	**p**
Cases	58 (100)	59 (100)	
Age (years 9) median	29	29.9	0.91
Range	24-39	22-.36	
First pregnancy	23)39.501)		
First trimester	29(50)		
Stage			
I-II	2 (3.0)	0	
III-IV	56 (96.111)	59 (100)	0.955
Histology			
Diffuse large B-cell	56(96.156)	55(9.320)	0.705
Burkitt-like	2(3.186)	4(6.778)	0.02
IPI:			
Low-low-intermediate	7 (11.800)	13 (22.035)	0.01
High-intermediate-High	51 (86.467)	46(77.900)	0.901
Treatment:			
CHOP	34(58.223)	36(161.56)	0.88
CHOP-R	24-(41.345)	23(38.967)	0.601
Complete response	51 (87.3555)	49 (84.490)	0.667
Obstetric complications	0		
Fetal complications			
Abortion			
Vaginal delivery	49(84.4)		
Ovarian failure	0		
Parenthood	32 (6 patients had 2 pregnancy)	12	
Outcome:			
PFS *	76% (95%CI: 70%-82%)	69%(95%CI58%-76%)	<0.01
OS*	87% (95%CI:79%-94%	70%(95%CI:61%-79%)	< 0.01
Children			
Preterm (< 36 weeks)	2 (3.00)		
Low-weight (< 2500 g)	7(22.212)		
Congenital malformations	0		

Abbreviations: IPI: International Project Index; CHOP: Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), R- CHOP (rituximab + CHOP), PFS: Progression-Free Survival; OS: Overall Survival.

curves at 10-years of PFS and OS were statistically better in pregnant patients with acute leukemia, Hodgkin lymphoma and diffuse Large B-cell lymphoma, compared with non-pregnant patients (Tables 1-3). We did not have any scientific explanation, to these differences, because pregnant and non-pregnant patients were treated with the same schedule of chemotherapy, obstetrical care, thus the probably protective role of pregnancy in patients with cancer, could did not have explanation, we hope that people that attended these setting of patients, revised these observation.

Univariate analysis to assess the any factor: age, treatment, socio-economic status, did no shot any statistically difference (data not show) only one woman developed mild symptoms of ovarian failure, that were treated. Second neoplasm or acute leukemia has not been observed.

Fetal complications: only 1 spontaneous abortion was observed. No congenital malformations were observed. Eight newborns (3.9 %) were preterm and 16 (7.9%) were low-weight; in all cases recovery were observed between 13 to 21 (median 12.4) days. These findings did not were associated with a worse

development. All children received the vaccination scheme, according to age; and severe health problems were not observed. Newborns and matched controls show a physical development according to the normal children in our country [13,14]. School attendance were evaluated, elementary and primary degree were finalized in all children, secondary degrees were finalized in 189 children (93.5%), high school grades were finalized in 156 children (77.2%), an university level was achieved by 106 children (52.4%) and post-graduated level was achieved in 45 cases (22.7%), no statistical differences in scholar attendance were observed with controls groups. When children became adult parenthood was normal, and they have 62 "second generation" children that were normal, however furthermore studies were not performed. Neurological development was considered normal, in both groups; no abnormality of neurocognitive studies was normal. Abnormal echocardiogram were observed in 3 children , but when the study was repeat it was normal, and remain until now thus, these abnormalities were considered false positives. Two children, died at 4 and 11 years, car accident, and scholar accident. Thus, 200 children are alive, healthy, with no late adverse events, including acute leukemia or second neoplasms.

DISCUSSION

Treatment of HM during pregnancy remain a challenge, because the common treatment included chemotherapy that is been considered to produce detrimental effect on a fetus during pregnancy, including congenital malformations, mutation, carcinogenesis, intrauterine growth restriction, mental retardation, low birth weight [19,20]. However, in most recent publications chemotherapy could be safely administered, but, most paper had a short follow-up (<5 years), with a low number of cases, and longer follow-up will be considered necessary, because some late adverse events, secondary to chemotherapy could be observed after 5 years of follow.

In our study, we have reported the clinical outcome of 202 cases with HM that were treated with chemotherapy, even during first trimester and a large follow. Pregnant and non-pregnant patients were with standard and more useful chemotherapy regimens that were administered at doses and schedules of each treatment, with minimal acute adverse events, adequate dose-intensity; obstetrical adverse events were minimal and did not affect the course of pregnancy. Both groups did not have severe adverse events, no cardiac toxicity was observed and second neoplasm or acute leukemia has not been observed. Surprisingly, a statistical difference in outcome was observed in pregnant patients, measured for PFS and OS compare with the no-pregnant patients, that were the control group that have the same HM, and we treated with the same chemotherapy. Some differences were observed when compared our results: during pregnancy the mother need an increase of proteins to maintain, neither of the multiple reports in this field mentioned the use of nutritional support, also supplemental vitamins, specially folic acid were also employed, thus the development of the fetus appear to be better, and low weight were less frequent and we considered than this fact permit a better fetal development. Also, this association increase fear anxiety in the mother, and most previous study did no mention the use of psychological support. In general obstetrical care is not mentioned, our patients were carefully treated, nutritional support, phsycological support, and clinical attention after delivery, had not mentioned in most papers, thus, we considered that the use of this support, may explain the best outcome in mothers and newborns and the mother and family had a better outcome. Moreover, most of papers in this field were informed in USA and Europe, with a racial predominance of white race, and the role of trace had did not considered in this setting of patients . Unfortunately we did not found reports of Latin America as geographic region, also Asian and Africans reports were not found.

In other hand, we confirm that the treatment of HM, including aggressive chemotherapy for the treatment of acute leukemia, or administered during first trimester, appear to be safely for the fetus, because no acute or late toxicities were detected. Physical development was similar to the control group, and inside the percentiles of Mexican children. Moreover, it has been reported that low-weight is frequent in newborns that received during pregnancy [9,19-21] could have abnormal development, but , in our population, low-weight was less frequent, and the children with lo-weight or preterm delivery have a physical, neurological, intelligence, and learning normal compared with the control group. Recently, Blommaert et al., conducted an elegant study to assess a neurological evaluation, using magnetic resonance imaging to assessed the possibility of neurological damage, they found any abnormalities, but, the children did not have any clinical evidence of damage [8], we considered that future evaluations with the same techniques, to observe if the changes will be increase or well disappears, and the most important if these image abnormalities can detect early clinical effects. Although the most important risk to the fetus were the administration of toxic chemotherapy associated to numerous late adverse events [21-24], most studies show that the possibility of acute or late events did are frequent; in our children we did not observed any acute or late adverse events, even when chemotherapy was administered during first trimester [7]. Moreover, it is appear that reported the capacity of this children when access to age of childhood, they can be have health children [23,24]. The unique difference that can observe is that we aggregated nutritional support to patients during pregnancy; we decided to this, because in our population malnutrition is frequent, and in diffuse large B-cell lymphoma it was a poor prognosis factor [25]; but, neither of the previous studied informed the nutritional status in mothers.

Another concern about the treatment of HM during pregnancy is the possibility that relapse could be most frequent [25], especially in Hodgkin lymphoma, however, relapse was similar in control group, thus, we considered that this possibility is not frequent. To treat this low incidence of adverse events has been suggested that influence the low number of toxicities in the fetus: increased blood volume and renal clearance that can decreased active drugs concentration, a faster hepatic mixed-function oxidase system might also cause lower drug concentration, changes in volume distribution peak drug concentration and half-life of administration changes during pregnancy, it has been observed that the ATP binding cassette (ABC) family ,predominately localized in the maternal fascial syncytial membrane placental microvilli comprise the major placental drug transporter active efflux of drugs by placental transporters help to maintain barrier function reduced the incidental adverse incidence of adverse events in the fetus [27,29]. It is evident

that the study have some bias, is a retrospective analysis, but we considered that prospective studies will be no-ethical, in the another hand, it is permit that the patients were treated with the same team, that files are available and longer follow-up of mothers an fetus was possible.

CONCLUSION

We present a review of our cases, with the longer follow-up reported, thus late events in mothers could be observed, and we could demonstrated that the use of aggressive chemotherapy during pregnancy, even in first trimester, was well tolerated, that the mothers show an increase in possibilities of cure, because more of 50 mothers had more of 20-years of follow-up, and believed that the possibility of relapse is remote. However, we considered that general rules are difficult to applied, and treatment in these setting of patients, will be the better available.

Contribution of authorship

Conception (AA, LS, SC); Planning (AA, SC); Carryout (AA, LS, SC); Analysis (AA, LS, SC), write the work (AA).

Ethical Statement

The work was approved by the Ethical and Scientific Committee of the Specialist Hospital, National Medical Center, on March 1975 (HE: 75/06), and modifications were approved by the same Committees on July 1081 (HE/81/011), and on September 1988 from the Committee of Ethical and Scientific from the Oncology Hospital, National Medical Center.

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