Pilot initiative in India to explore the gonadal function and fertility outcomes of a cohort of childhood cancer survivors

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ABSTRACT

CONTEXT: Steady improvement in childhood cancer outcomes has led to a growing number of survivors, many of who develop long-term sequelae. There is limited data about these sequelae (including those related to fertility) on childhood cancer survivors from India. **AIMS:** We undertook a prospective pilot study on childhood cancer survivors from India to assess their gonadal function and fertility. **SUBJECTS AND METHODS:** A pediatric oncologist and a reproductive medicine specialist assessed 21 childhood cancer survivors. The risk of infertility was established using disease and treatment variables. Current status of puberty, sexuality, and fertility were assessed using clinical and biochemical parameters. Outcomes were correlated with risk group of infertility. Information was also ascertained on counseling with regards to risk of infertility. **RESULTS:** The cohort included 21 survivors (71% males) with a median age of 18 years who were off treatment for a median age of 7 years. Ten (48%) survivors were at low risk for infertility, 9 (43%) at medium risk and 2 (9%) at high risk. Gonadal dysfunction was seen in 3 (14%) survivors: 0/10 (0%) low risk, 1/9 (11%) medium risk, and 2/2 (100%) high risk. None of the survivors, who are at high risk or medium risk of infertility, received any counseling before treatment. **CONCLUSIONS:** This prospective pilot study of a cohort of childhood cancer survivors from India demonstrates a deficiency in the information provided and counseling of patients/families at the time of diagnosis with regards to the risk of infertility. Fertility outcomes of childhood cancer survivors were congruent with recognized risk groups for infertility. Future action points have been identified.

KEY WORDS: Childhood cancer, fertility, late effects, India

INTRODUCTION

There has been a steady improvement in childhood cancer outcomes. In high-income countries like the USA in the 21st century, for every 10 children diagnosed with cancer, eight would be alive 5 years after diagnosis.[1] There are nearly 400,000 childhood cancer survivors alive in the USA today[2] and the focus is increasingly on the need to reduce treatment-related sequelae in these survivors.[3] Treatment of childhood cancer has a deleterious effect on subsequent gonadal function and fertility of male and female survivors.[4-6] Exposure to alkylating agents and radiation therapy are key factors associated.

Much of our knowledge in this area comes from the research in high-income countries. There is limited data from India on childhood cancer outcomes[7] and an even greater paucity of information on late effects.[8,9] A recent study by Rajendranath *et al*. on long-term sequelae in 155 pediatric cancer survivors from Chennai reported gonadal dysfunction in nearly a quarter of the cohort although the analysis was limited.[9] Hitherto, it remains the only published study from India related to this field.

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Cankids is a grass-root level national society of over 225 individuals (volunteers and employees) committed to making a change for childhood cancer in India and currently works in 42 cancer centers across India. A focused group discussion in November 2013 with childhood cancer survivors and parents of childhood cancer survivors, all of who work for Cankids revealed a significant lack of awareness of issues related to fertility. Moreover, none of the survivors had any assessment of their health status in this regard. We undertook a pilot study on these childhood cancer survivors to assess their gonadal function and fertility and consequently take one step in bridging the knowledge gap, which exists in India.

METHODS

This was a prospective pilot study of a cohort of 21 childhood cancer survivors who were members of Kidscan Konnect – the survivor group of Cankids or children of Cankids parent support group members. Informed consent was taken from the survivors and/or parents. They were invited to attend a monthly late-effects clinic focused on fertility, which was held from December 2013 to March 2014. A pediatric oncologist and a reproductive medicine specialist saw each survivor. Along with demographic information, data were collected on cancer diagnosis and treatment received including details of exposure to alkylating agents and radiotherapy. Based on this information, stratification for risk of infertility (low, medium, and high) was done.[10,11]

To ascertain the current status of puberty, sexuality and fertility in survivors, clinical evaluation in the form of history and physical examination was done. This was complemented with laboratory tests as follows: Semen analysis by physical examination and microscopy in the postpubertal male survivors and antiMullerian hormone (AMH) levels by enzyme immunoassay in postpubertal female survivors. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were ascertained by chemiluminescent immunoassay and testosterone levels (in males only) by radioimmunoassay in the prepubertal male and female survivors as well as the postpubertal male survivor who was unable to provide a semen sample. Gonadal dysfunction in males was diagnosed based on abnormal semen analysis or hypergonadotrophic state (high LH and FSH). In females, gonadal dysfunction was diagnosed based on low AMH or hypergonadotrophic state (high LH and FSH).

Finally, the cohort of survivors and their parents were also asked about any counseling with regards to risk of infertility which was done at diagnosis and before initiation of cancer treatment.

RESULTS

Baseline information

The cohort included 21 survivors (71% males) with a median age of 18 years (range 13–30 years) who were off treatment for a median of 7 years (range <1–16 years). Original cancer diagnosis were acute lymphoblastic leukemia (ALL) in 10 children (including two relapses), non-Hodgkin lymphoma in three children, acute myeloid leukemia in two children, and one child each with Hodgkin lymphoma, retinoblastoma, Wilms tumor, Ewing sarcoma, osteosarcoma, and ovarian germ cell tumor.

Gonadotoxic exposure

Overall 14 (67%) survivors were exposed to alkylating agents, which most commonly was cyclophosphamide with a median cumulative dose of 3000 mg/m^2 (range 900–6600 mg/m^2). Furthermore, 10 (48%) survivors were exposed to radiotherapy, all of whom had ALL and were given 18 Gy of cranial radiotherapy and one patient who had ALL with testicular relapse was given testicular radiation. One survivor had gonadal surgery for ovarian dysgerminoma. None of the survivors had undergone hematopoietic stem cell transplantation.

Infertility risk stratification and gonadal failure

Based on clinical and treatment variables 10 (48%) survivors were classified as low risk for infertility, 9 (43%) as medium risk and 2 (9%) as high risk [Table 1]. Median FSH levels (n = 13) were 5.2 mIU/ml (range 0.76–29.59), median LH levels (n = 13) were 3.7 mIU/ml (range 0.26–20.76). In males, the median testosterone levels (n = 9) were 9.16 ng/ml (range 0.5–25.75) and in females, the median AMH levels (n = 4) were 3.5 ng/ml (range 2.18–4.37). Oligospermia as defined by WHO criteria was identified in one of the four semen analyses done. These investigations established that gonadal dysfunction was seen in three of the 21 survivors (14%). The two survivors

Table 1: Summary of gonadal function outcomes when stratified by risk group

Risk group	Diagnosis	Total	Gonadal dysfunction (%)
High	ALL with testicular relapse 1 Ewing sarcoma 1	2	2 (100)
Medium	NHL 3 AML 2 ALL with relapse 1 Hodgkin lymphoma 1 Gonadal GCT 1 Osteosarcoma 1	9	1 (11)
Low	ALL 8 Retinoblastoma 1 Wilms 1	10	0 (0)

ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, GCT=Germ cell tumor, NHL=Non-Hodgkin lymphoma

at high risk of infertility also had biochemical evidence of gonadal failure. One of the four survivors at medium risk had evidence of gonadal failure while none of the survivors at low risk had gonadal failure [Table 1].

Counseling about risk of infertility prior at diagnosis

Only three survivors (15%) of the cohort had been told were told about the possible risk of infertility as a result of treatment. None of the survivors or their parents received any counseling on options of fertility preservation, and this included those survivors who were at high risk or medium risk of infertility, also, none of the four children who were postpubertal at diagnosis were informed about the risk of infertility or offered any fertility preservation options. Following the end of treatment, issues related to sexuality and fertility had not been discussed.

DISCUSSION

This prospective pilot study of a cohort of childhood cancer survivors from India, which focussed on fertility, allows us to make some important inferences. First, it demonstrates a deficiency in the delivery of optimal care. This deficiency is at two levels; at the time of diagnosis when there is the absence of counseling of fertility related issues for children with cancer in India, and subsequently for survivors with limited access to late effects clinics and lack of information, counseling, and investigations. This observation contrasts with the practice in Europe where there is a much greater awareness of the potential adverse effects of therapy on fertility as well as higher referral rates for fertility preservation, particularly in postpubertal boys.[12,13]

Second, our study suggests that the chance of occurrence of gonadal dysfunction in our population was congruent to the stratification for risk of infertility (low, medium, high).[10,11] None of the low-risk group survivors had a gonadal failure, whereas all the high-risk group survivors had a gonadal failure. Such information is useful to plan judicious allocation of resources to tackle fertility preservation either at diagnosis or at the end of treatment, particularly in resource-limited settings like ours.

The main limitation of our study was the small sample size and the self-selected nature of the cohort. All our observations would ideally need to be confirmed on a larger cohort and proposal for this are being formulated. As none of the survivors were married and/or sexually active it was not possible to comment on the chances of conceiving or siring a pregnancy in the case of female and male childhood cancer survivors, respectively.

Importantly, several action points emerged out of the work carried out in this pilot. It provided reassurance to the majority of survivors who did not have gonadal dysfunction. Furthermore, it identified those with gonadal dysfunction, and appropriate counseling and fertility preservation options have been offered to these survivors. Cankids has now created information, education and communication material on fertility risks for patients as well as survivors [Figure 1].

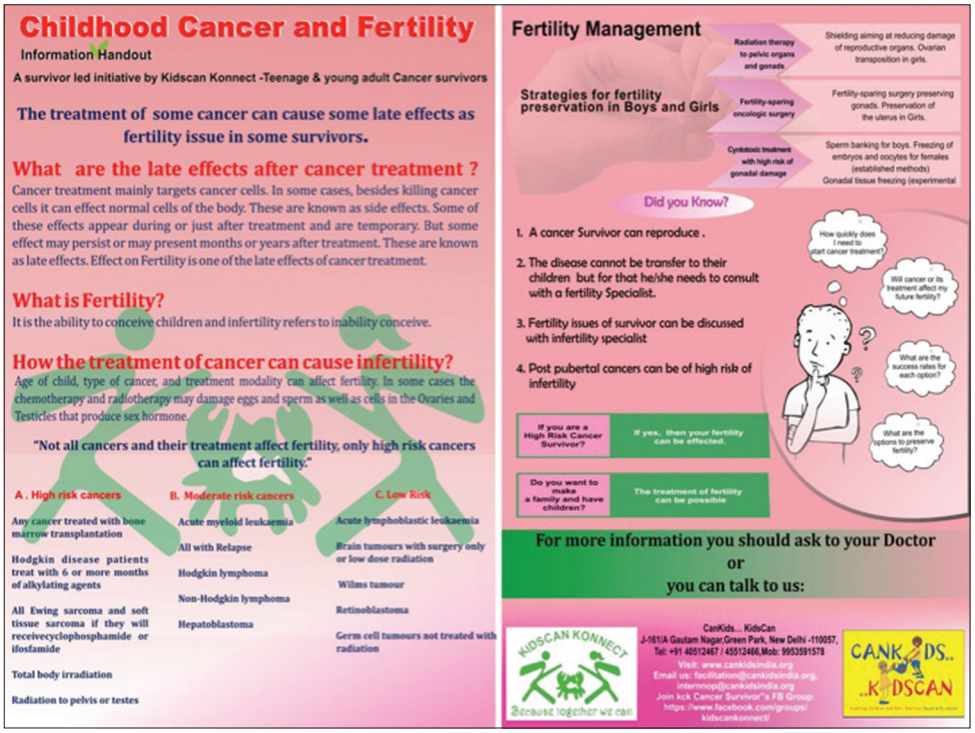

Figure 1: Information, education, and communication material developed on childhood cancer and fertility

The Cankids social support team is being trained to share this information and counsel those at higher risk. Along with imparting information, options for sperm banking and oocyte cryopreservation for postpubertal patients are being explored including an assessment of costs.

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Conflicts of interest

There are no conflicts of interest.

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