Treatment of high risk Sertoli-Leydig cell tumors of the ovary using a gonadotropin releasing hormone (GnRH) analog

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Sertoli–Leydig cell tumors are rare ovarian neoplasms. We report two unusual cases with bilateral SLCTs suggesting evidence of genetic predisposition and at high risk of recurrence. To reduce this risk, we exploited the use of GnRH analog to lower gonadotropin and potentially directly inhibit the tumors through expressed GnRH receptors. We used it as maintenance antitumor therapy for 2 years after completion of chemotherapy, to cover the period of risk for recurrence. Both patients remain in complete remission at >2 years after completing leuprolelin therapy. Of note, both patients carry DICER1 mutations, frequently found in pleuropulmonary blastoma syndrome. Pediatr Blood Cancer 2013;60:E16–E18.

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acetate according to the same schedule as case 1 after completing four courses of chemotherapy. The interval between injections was reduced to 6 weeks in order to keep LH and FSH levels fully suppressed. She completed 2 years of this therapy and hormone replacement therapy was commenced similar to case 1. She remains in complete remission at 4 years from diagnosis and 30 months after completion of GnRH therapy. The one abnormal inhibin A level measured during follow up was ascribed to a laboratory error and subsequent levels were normal (Fig. 1B).

**Detection of GnRH Receptors**

The receptor binding studies were conducted on frozen tumor from case 1 [6]. Membranes from a HEK293 cell line stably expressing the GnRH receptor (SCL60) and rat pituitary were used as positive control and liver membranes as a negative control. Two separate samples of Case 1 tumor showed specific binding of radiolabelled GnRH analog as did SCL60 and pituitary (Fig. 1C and D).

**DISCUSSION**

There are few data in the literature on risk-adapted therapeutic strategies in ovarian sex cord stromal cell tumors in children. Schneider et al. [4] described 54 cases documented prospectively and defined risk groups with respect to stage; completeness of resection; histologic appearance, such as differentiation and proliferative activity of the tumor. Surgery remains the mainstay of initial management. Cisplatin based chemotherapy constitutes an important role as adjuvant therapy for those patients with SLCT stage I, poorly differentiated and those containing heterologous elements.

In 1975, Stadel [7] proposed the "gonadotropin theory," hypothesizing that exposure to high gonadotropin levels favor malignant transformation. SLCTs express receptors for follicle stimulating hormone (FSH) which has been shown to support the growth of granulosa cell tumors in nude mice [8]. GnRH analog therapy at high doses can act to suppress the receptor activity and has been suggested as treatment for progressive ovarian tumors that have failed to respond to chemoradiation [9]. The apparent efficacy of GnRH analog in our SLCT patients which lowered gonadotropins may support this theory. There may have also been direct antiproliferative effects as described in a number of reproductive tissue cancers, including ovarian cancer [10–15]. Although there are case reports about the use of GnRH analog for SLCTs of the ovary in adults [16], no data have been reported in children. Whilst we could not demonstrate tumor response in the absence of measurable disease or raised tumor markers, we are encouraged by the duration of clinical remission in both patients and their lack of problems on introduction of hormone replacement therapy.

Fig. 1. Case 1 inhibin A and B levels (A) and case 2 AFP, inhibin A and B levels (B) [normal range—inhibin A in premenopausal women varies with the cycle <7–69 pg/ml and inhibin B in girls aged 11–12 years as per Women and Infants Hospital, Rhode Island, US is —<10–186 pg/mol. Alfa-fetoprotein (AFP) is <10 ku/L]. GnRH receptor study on the case 1 specimen (C) [cell line SCL 60 expressing GnRH receptor, pituitary membranes as positive control and liver membranes as a negative control. The second column of each is the non-specific binding (10^{-6} M ligand). Both tumor specimen A and B had specific binding]. Dose–response binding curve of cell membranes of case 1 specimen demonstrating high affinity binding sites suggestive of GnRH receptors (D).
Recent advances in the understanding of the genetics of SLCTs have provided insight into the unusual clinical phenotype in the two cases presented here. Both were included in a study of the rare pleuropulmonary blastoma syndrome of which SLCTs have recently been shown to form part of the spectrum [17]. This syndrome is due to constitutional heterozygous mutations in the DICER1 gene, the master regulator of micro RNA production. Both cases presented had constitutional DICER1 mutations. DICER1 mutations can cause a range of phenotypes from asymptomatic to various tumors such as cystic nephroma, pleuropulmonary blastoma, thyroid cysts, SLCTs, and Wilms tumor. Case 2 also has thyroid cysts, now recognized as part of the DICER1 syndrome [17].

In conclusion, the prolonged remission in two cases presented here suggests that GnRH analogs may have a therapeutic role in high risk SLCTs. While we do not have direct evidence for the efficacy of GnRH analogs with potential influence of high dose therapy and stem cell rescue on case 1, our findings set the scene for further studies for maintenance therapy using GnRH analogs in SLCTs.

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REFERENCES