Anxiety And Depression Problems in Women Having Ovarian Germ Cell and Sex Cord Stromal Tumors

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Abstract: Gynaecological cancers are relatively frequent in the female population. Malignant sex cord-stromal tumours are rare and include granulosa cell tumours (most common) and Sertoli-Leydig cell tumours; they are typically associated with a good prognosis. Most of the patients with granulosa tumours present with early-stage disease. The disease is typically indolent. Patients with stage IA or IC sex cord-stromal tumours desiring to preserve their fertility should be treated with fertility-sparing surgery. The standard treatment mainly involves conservative surgery combined with chemotherapy depending on the stage and the prognostic factors, as for testicular cancers. As reported in testicular cancer survivors, chemotherapy may induce sequelae impacting quality of life, which has not yet been evaluated in survivors of germ cell tumors and sex cord stromal tumors.

Key Words: — ***Tumors, necrosis, DICER1, STK11.***

I. INTRODUCTION

Ovarian sex cord-stromal tumors are uncommon neoplasms that typically present in the first two to three decades of life, with the exception of adult granulosa cell tumors, which typically present later, with risk for development peaking at age 50 to 55 years [1]. In aggregate, these tumors account for approximately 5% of ovarian malignancies in women age 15 to 24 years. Initial evaluation should include a thorough history with careful attention to any individual or family history of possible tumor predisposition as well as physical examination with attention to presence of precocious puberty or delayed menarche, hyper pigmented macules that are suggestive of Peutz-Jegher, or thyroid nodules that are suggestive of DICER1 syndrome [2]. Tumors are often large at diagnosis and may rupture, which can result in an acute presentation with hemoperitoneum. These tumors are typically unilateral, 10 to 15 cm in greatest dimension, and may vary from solid, firm, and lobulated to soft and friable, often with hemorrhage and/or necrosis [3].

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In one review of 72 pediatric patients with sex cord-stromal tumors, juvenile granulosa cell tumors and Sertoli-Leydig cell tumors together accounted for 85% of such neoplasms in children and adolescents. The capsule of the ovary is intact in most cases, which accounts, in part, for the excellent outcome; however, in tumors with rupture or invasion beyond the capsule, juvenile granulosa cell tumors can pursue an aggressive clinical course [4]. Adult granulosa cell tumor is uncommon in children just as juvenile granulosa cell tumor is uncommon in adults. Sex cord tumors with annular tubules are a distinctive histologic category and show tubules with Sertoli cells arranged around one or more hyaline bodies. In patients with Peutz-Jegher syndrome, these tubules may be scattered and admixed with normal ovarian tissue rather than forming a distinct mass [5]. Recent analyses have reshaped our understanding of the pathophysiology of some of these tumor subtypes. Mutations in DICER1, STK11, and FOXL2 influence the development of some of these neoplasms. DICER1 encodes an endonuclease that is critical for microRNA processing. DICER1 mutations are associated with pleuropulmonary blastoma, which is the most common lung tumor of infancy and early childhood, as well as with embryonal rhabdomyosarcoma of the uterine cervix, renal tumors, thyroid nodules and carcinoma, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma, pineoblastoma, and pituitary blastoma [6]. Biallelic loss of function and missense RNase IIIb DICER1 mutations result in systemic loss of 5p-microRNAs

that precludes regulation of growth-promoting gene programs. Testing for DICER1 mutations may have important implications for individuals and familial tumor risk and may facilitate diagnosis of associated conditions. Of importance, individuals with tumor predisposition are at risk for development of contralateral, metachronous ovarian tumors after the general risk for recurrence has passed and, thus, prolonged monitoring is recommended in this setting [7]. Sex cord-stromal tumors with annular tubules may be associated with Peutz-Jegher syndrome and specifically with mutations in the STK11 gene. Individuals with clinical findings of Peutz-Jegher syndrome should undergo genetic testing that includes screening for deletion and/or duplication of STK11 and relevant organ-specific screening [8]. Ollier disease includes enchondromatosis, whereas Mafucci syndrome includes enchondromatosis and hemangiomas. Enchondromas may be associated with bony deformities and chondrosarcomas. Somatic mosaic mutations in IDH1 and IDH2 may be observed. New analyses of FOXL2 and clinical outcomes may alter the clinical approach to these generally indolent tumors [9].

II. Initial Treatment And Preoperative Preparation

When an ovarian sex cord-stromal tumor is suspected, levels of inhibin, estradiol, testosterone, and AFP should be obtained. Inhibin levels may be elevated in granulosa cell tumors; inhibin B may be more predictive than inhibin A. Granulosa cell tumors may also present with elevated estradiol, and Sertoli-Leydig cell tumors may present with elevated testosterone or, rarely, AFP [10]. Ultrasound is the most common initial imaging modality. A large mass is commonly seen. Cross-sectional imaging, either computed tomography or magnetic resonance imaging, may show an adnexal mass with a heterogeneous appearance. As in other ovarian tumors, laterality may be difficult to determine from initial imaging and is best determined intraoperatively [11]. Fertility-sparing surgery is preferred in children, adolescents, and women of reproductive age as long as the contralateral tube and ovary and the uterus are unaffected, which is usually the case. Fertility-sparing surgery does not refer to ovarian cystectomy alone, but implies the complete removal of the affected adnexa. Women who are past reproductive age usually undergo total hysterectomy and bilateral salpingo-oophorectomy. Comprehensive staging includes sampling of peritoneal fluid, examination of the contralateral ovary, biopsies of the peritoneum and any suspicious lesions, omental biopsy, and palpation of lymph nodes, with resection of any lymph nodes that have concerning features upon imaging or intraoperative examination. Complete lymphadenectomy is typically excluded from the procedure, as the risk of nodal metastasis with primary disease is low [12]. If confirmed as FIGO stage Ia, most tumors may be treated with surgical resection alone. Tumors that are staged higher than Ia may require chemotherapy and/or additional surgery. Treatment with cisplatin, etoposide, and bleomycin over 5 days, usually for four cycles, is often administered to children and adolescents in the United States who require chemotherapy. In Europe, treatment with cisplatin, etoposide, and ifosfamide is more common [13]. In adult patients, the standard of care has been considered bleomycin, etoposide, and cisplatin, but evidence suggests that paclitaxel and carboplatin have activity in this setting and may be equivalent and less toxic. Recurrent disease may be treated with surgery, but other modalities have efficacy. Radiation therapy may be useful in settings of recurrent disease. Bevacizumab has also shown activity and provides another option for treatment, either alone or in combination. Separate from recurrent disease, in some individuals—for example, those with Sertoli-Leydig cell tumor in the context of predisposing DICER1 mutations—there is a risk of metachronous, contralateral Sertoli-Leydig cell tumor[14]. These metachronous tumors are generally identified as stage Ia and are often treated with surgery alone.

III. Results

The main objective is to assess chronic fatigue in survivors treated for ovarian GCT or SCST with surgery and chemotherapy compared with patients treated with surgery alone and with age-matched healthy women (± 2 years). All participants are asked to complete several validated self-reported questionnaires including standardized and validated questionnaires. Patient's medical data (date and context of disease diagnosis, treatment modalities, fertility-sparing, second cancer, and comorbidities (focus on cardiovascular diseases, pulmonary and metabolic disorders)) are collected from patient records. For the healthy control group, the website administrator of the Seintinelles network publishes the study information and the questionnaires on their website, and contacts registered healthy women to complete the different questionnaires online. Once signed informed consent has been obtained, patients undergo cardiovascular, respiratory, hearing, metabolic and hormonal work-up.

3.1 Cardiac check-up which will include:

A cardiac consultation including the measurement of systolic pressure index; An electrocardiogram; Carotid Doppler ultrasound with measurement of carotid intima media thickness and arterial; vasoreactivity (arterial elasticity, carotid pulse wave velocity) (optional for vasoreactivity), A capillaroscopy: search for Raynaud's syndrome (optional); A humeral Doppler ultrasound for study of flow-mediated humeral vasodilatation (optional); A trans-thoracic echocardiography 2D, 2D Strain (optional) and ± 3D; A blood test comprising an enzyme profile: ultra-sensitive troponin, BNP, von Willebrand factor assay, and t-PA.

Lung and hearing examination: Respiratory Function Tests (RFT); Tonal audiogram.

3.2 Blood sampling:

Exploring metabolic and hormonal disorders. Carbohydrate-lipid balance: fasting blood glucose and insulin, lipid fractions, triglycerides; Hepatic: transaminases (TGO, TGP), Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Alkaline Phosphatase (PAL), Gamma-glutamyl transferase (GGT), Lactate dehydrogenase (LDH); Hormone balance: sex hormone binding globulin (SHBG), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Estradiol, Anti-Müllerian hormone (AMH), thyroid stimulating hormone (TSH). Osteocalcic balance: calcium, phosphorus, vitamin D; Renal assessment: ionogram, creatinine; C-reactive protein (CRP) + highly sensitive CRP. Compensation is offered to cover the costs of transport and to compensate one day off work.

The first aim is to show a difference in the proportion of patients with chronic fatigue (≥1 dimension of MFI-20) in the group of interest as compared with each of the control groups. The pairwise comparison will be performed using the $\chi 2$ test (one-tailed test under the assumption of higher chronic fatigue in the chemotherapy group of interest) at a risk $\alpha = 0.05$ and a power level of 80% ($1-\beta = 80\%$). Assuming that 25% of patients express chronic fatigue in the group of interest as described in testicular cancer [11-18] and 10% in each of the control group, the required sample size, with a 2:1 allocation ratio in favor of the group of interest, is 121 subjects in the group of interest and 61 subjects in each of the two control groups (patient control and healthy control). To anticipate 10% of non-assessable women, we plan to enroll 134 survivors in the group of interest, 67 survivors in the control group, and 67 healthy controls.

IV. Discussion

This study will provide important data on the potential long-term physical side-effects of chemotherapy in survivors of Germ Cell Tumors (GCT) and Sex Cord Stromal Tumors (SCST), especially cardiovascular and pulmonary disorders, and neurotoxicity [15-19]. The identification of long-term side-effects can contribute to adjusting the treatment of ovarian GCT or SCST patients and to managing follow-up with adapted recommendations regarding practices and chemotherapy regimens, in order to reduce toxicity while maintaining efficacy. Based on the results, intervention strategies could be proposed to improve the management of these patients during their treatment and in the long term [16-20].

V. Conclusion

Ovarian sex cord-stromal tumors are underreported but clinically significant neoplasms. As a result of coding and reporting issues, these tumors are often not reported to state or national cancer registries. These methodologic limitations do not reflect our current understanding of the biology and clinical relevance of these tumors. A /1 ICD-O behavior code may result in underestimation of risks. For example, with Sertoli-Leydig cell tumors, careful staging and assessment of level of differentiation is required to determine whether adjuvant therapy is needed [17,18]. Referral to an oncology specialist for evaluation, possible treatment, surveillance, and a discussion of potential genetic implications is recommended. In addition, limitations in national reporting prevent an epidemiologic understanding of these tumors, including the risk for subsequent malignancies. Reconsideration of the criteria for the inclusion of these tumors in national cancer registries would allow for a more population-based approach to the study of sex cord-stromal neoplasms [20-25]. Benefits would include the ability to calculate true incidence and survival rates, which, given the long interval to recurrence of these tumors, is difficult to determine from single-institution analyses. Another benefit would be the determination of any geographic or racial and/or ethnic differences in incidence. Changes to coding designations would facilitate clinically relevant epidemiologic investigations [26-29]. Including all Sertoli-Leydig cell tumors, juvenile granulosa cell tumors, and gynandroblastomas in national registries through one or both of the above modifications will allow accurate tracking of

incidence as well as subsequent neoplasms to aid in the understanding of the full spectrum of disease [30-33]. As cancer epidemiologic investigations advance, it is critical to understand not only what is histologically malignant, but also what is clinically significant and what will ultimately contribute to our understanding of the impact of cancer and its therapies [34-36].

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