Sex cord-stromal tumours, rare events in oncology necessitating multidisciplinary approach and referral pathways

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Summary

Tumours of the stroma (Leydig cells) and/or sex cords (Sertoli cells) represent approximately 8% of ovarian tumours and develop from the conjunctive tissue (respectively, interstitial and nurse cells) of the ovaries. Because these cells participate in ovarian hormonal function, most of the sex-cord or stromal tumours are able to secrete hormones (oestrogens, androgens, corticoids), which explains the hormonal dysfunctions associated with these cancers.

Their prognoses are difficult to establish; some of the tumours are almost always benign (Sertoli cell tumours, Leydig cell tumours), whereas others are malignant but with variably delayed local–regional, or metastatic relapses. The histological criteria of aggressiveness are so poorly known that it is difficult to even propose a dichotomous, benign–malignant histopathological classification. If they do not present clinical criteria of 'malignancy', these tumours are considered to be of uncertain prognosis. In this group of tumours, the following might have 'malignant' behaviour: Granulosa cell tumours, androblastomas (or Sertoli–Leydig cell tumours), tumours of the sex cords with annealed tubules, tumours of the steroid-producing (theca) cells without any other specification, and fibrosarcomas. Surgery is the most important therapeutic modality and must be as conservative as possible to preserve reproductive function; it can be effectively combined with chemotherapy for advanced stages.

Introduction

'Non-epithelial malignant tumours of the ovary are rare cancers for which the natural history is not well known and for which prognostic factors are still to be elucidated; for these reasons all patients should be referred to specialised centres with a specific interest in this type of tumour and adequate department of pathology' [1].

Indeed, sex cord tumours (SCTs) are rare cancers of the ovarian area in adults. They represent less than 8% of all adult ovarian tumours [2]. Sex-cord stromal tumours are a heterogeneous group of tumours that develop from the sex cords and the ovarian stroma. These tumours are detected typically at an early stage, and they may recur as late as 30 years after the initial treatment. SCTs can occurs as an isolated histological tumour type or in combination with other tumour types, but together, they account for only 7% of all ovarian malignancies (Table 1). Currently, their treatment is defined as follows:

- the surgical approach is based on that of ovarian epithelial tumours, with one major difference: preserving the fertility, since these tumours arise in younger women [2,3].
- Chemotherapy for these tumours is based on that of testicular germ cell tumours [4].
- Surgery, chemotherapy and a surgical approach to residual masses are combined.

Surgery, which remains a vital step in therapy, could be combined with chemotherapy and must attempt to preserve fertility [5]. The effect of chemotherapy must be taken into account when deciding on a new intervention, which appears necessary in isolated cases. Nevertheless, malignant non-epithelial tumours of the ovary are rare cancers for which natural history is not well known and for which prognostic factors are still unclear [6], and this is why these patients should be referred to specialised institutions with a specific interest in these rare tumours and the subsequent department of pathology. Indeed, recent studies report that aside from the tumour stage, the number of cases

Table 1
Histological types of sex cord tumours with potential malignant behaviour

Sex cord-stromal tumours
Adult granulosa cell tumours
Juvenile granulosa cell tumours
Fibro-thecal tumours
Sertoli-Leydig cell tumours
Gynandroblastoma
Fibrosarcoma
Steroid cells tumours
Sex cord tumour with annular tubules

treated both in surgical and medical departments has prognostic significance [7].

Granulosa cell tumours

Abstract

Granulosa cell tumours represent approximately 2–3% of ovarian cancers. Adult granulosa cell tumour is the most common malignancy among the sex-cord stromal tumours. The prognostic factors that are related to survival have not been well defined. The overall prognosis is favourable with long-term survival ranging from 75% to 90% for all stages. However, tumour stage represents the most important clinical parameter of prognostic relevance [8]. The associated endocrine manifestations are often oestrogenic. Surgery remains the cornerstone of treatment for both primary and recurrent disease. Surgery is the most important therapeutic arm, with excision of all lesions as the fundamental of treatment, but surgery conserving reproductive functions is often possible at early stages for young patients. Conservative surgical approach with unilateral salpingo-oophorectomy seems to be reasonable for patients wishing to preserve their fertility, after careful staging, and in the absence of extraovarian spread. These tumours are chemosensitive and the highest response rate (>60%) is obtained with BEP (cisplatin, etoposid, and bleomycin) [9]. Two serum markers: oestradiol and inhibin, seem to be useful for monitoring relapses. Granulosa cell tumours are often slowly progressive and can relapse late (at a mean of 6 years).

Definition

Granulosa cell tumours are malignant tumours of sex cord and stromal origin. Two histological forms are known: juvenile (rare, young patients, early isosexuality, associated breast cancer, good prognosis) and adult (hyperoestrogenism, associated with endometrial hyperplasia and uterine carcinoma, high tumour mass, the most common (95% of granulosa cell tumours). The etiology of GCT is unclear. Although the excessive stimulation by gonadotrophin in the context of treatment for infertility has been reported to increase the risk of developing GCT, this has not been borne out in other studies [10]. One approach to understanding the molecular pathogenesis of CGT is to take the available information about gene expression in normal cells as basis for analysing signalling systems in these tumours. The patterns of many granulosa cell genes expressed through folliculogenesis have been characterised. The most active phase of granulosa cell proliferation occurs between the preantral and preovulatory stages. Proliferation is induced by FSH, a response that requires both insulin-like growth factor I (IGF-I) and oestrogen action [11]. It is also modulated by members of the TGF-β superfamily [12]. The mechanisms that regulate this phase of granulosa cell proliferation have been reviewed recently [13].

Frequency/incidence

Granulosa cell tumours represent 2–3% of ovarian cancers and are the most common malignant tumours in the group of sex cord and stroma tumours.

Clinical description

Granulosa cell tumours almost always contain granulosa and thecal cells; the endocrine manifestations associated with them are often oestrogenic.

Disease progression

Granulosa tumours are often slowly progressive and could relapse late (at a mean of 6 years). Relapses occurring 20 or 30 years after the first treatment have been reported for 5% of the patients in relapse. However, certain aggressive forms relapse and progress more rapidly [7].

The International Federation of Gynaecology and Obstetrics (FIGO) stage [8], intraperitoneal tumour rupture and bilateral tumours are the most often reported factors of prognosis. The patient's age and the size of the tumour (>5 cm) have a less certain prognostic value [14].

Among the cytological factors, the number of mitoses has the highest prognostic value, with prognosis being worst beyond five or ten mitoses per ten high power fields (HPF). Cellular atypia and poor differentiation (rarity of Call–Exner bodies) have a lower prognostic value [15]. Markers of cell proliferation (ploidy, DNA content) and expression of p53, c-myc or c-erb B2 have no proven prognostic value and remain controversial [16,17].

Management

Surgery

Because 70% of the patients present with stage I tumours, surgery represents the most important therapeutic arm [14]. Its role is essential but no precise recommendation can be given concerning its modalities: excision of all the lesions remains the foundation of therapy. For early-stage tumours, conservative surgery, preserving the possibility of a future pregnancy, can often be performed. Otherwise, it is reasonable to perform a total hysterectomy with bilateral annexectomy [18]. Concerning the impact of nodal dissection, very few data are available without clear information concerning the retroperitoneal nodes involvement for granulosa tumours [19].

For young women who can be offered conservative therapy, uterine curettage should be performed before surgery, because of the frequent association of tumours of granulosa origin with endometrial hyperplasia (55%) or endometrial adenocarcinoma (4–20%) [20].

Finally, the long natural history of the disease may lead to repeated surgery should a relapse occurs.

Radiotherapy

Granulosa cell tumours are radiosensitive but the role of radiotherapy has not yet been defined: the volume to be irradiated has not been determined, the radiation doses are not specified and no data are available on survival after radiotherapy. *Little evidence exists for the use of radiation or hormone therapy, and these modalities should be restricted to selected cases*.

Chemotherapy

The chemosensitivity of these tumours has been demonstrated by the numerous responses observed in the context of palliative therapy: responses of short duration to alkylating agents, frequent responses to adriamycin-bleomycin, actinomycin-fluorouracil-cyclophosphamide combinations added to cisplatin. The highest response rate (80%) was obtained with PVB (cisplatin, vinblastine and bleomycin). However, since 1993, with Colombo publication on BEP, this chemotherapy programme became the standard in first line intention [9]. Platinum-based chemotherapy is currently used for patients with cancer in advances stages or recurrent disease, with an overall response rate of 63% to 80%. There are no data to support any kind of postoperative adjuvant treatment for patients with stage I sex-cord stromal tumours, given the indolent nature of these neoplasms and the overall good prognosis (9% of relapse risk). Adjuvant chemotherapy should be reserved for advanced (stage II to IV) and recurrent disease. The benefit for stage Ic remains uncertain.

In 2005, GOG published retrospective data (from 1985 to 2002) about BEP versus carboplatin plus taxanes (docetaxel or paclitaxel) in first line or recurrent disease for sex cord-stromal ovarian tumours. Eleven patients in first line received BEP program and 11 taxanes–carboplatin programme. There is no statistical difference in term of response rate, progression free survival or overall survival in this short series. Among patients treated for recurrent disease ($n = 10$ for BEP, 37 for taxanes groups) the response rate was higher for BEP-treated (71%) than for taxanes-treated patients (37%), but this was not statistically significant. In all patients treated for recurrent disease, there was no significant difference in failure to progress at chemotherapy completion between BEP (70%) and taxanes-treated patients (62%) or in median PFS (11.2 versus 7.2 months). Taxanes demonstrated an interesting activity in sex-cord stromal tumours with a favourable toxicity profile. Taxane and platinum combination chemotherapy seem to be a reasonable candidate for future trials. To complete this observation we are currently investigating on the French language website observatory (www.ovaire-rare.org) the benefit of the association of docetaxel plus gemcitabine (uterine leiomyosarcoma program [21]) for sex cord stromal tumours refractory or in relapse to BEP program.

Future perspectives

Granulosa cell tumours of the ovary arise from granulosa cells of the ovary on morphological, biochemical and molecular analysis. In order to understand the molecular pathogenesis of these tumours, different activating mutations of the signalling pathway are under consideration [22]. The better understanding of characterisation of signalling pathways known to be important in the regulation of granulosa cell growth and differentiation could delineate new targets for treatment and so new opportunities of targeted treatment for these rare tumours. In this way, activating mutation of the FSH-signalling pathway and their oestrogen receptor expression could explain the resistant of GCT to inhibin [13]. As with other solid tumours, GCTs of the ovary probably occurs as a series of acquired somatic mutations. It seems logical that these will occur in pathways that are important in the regulation of growth, differentiation and apoptosis of normal granulosa cells. Recent studies have eliminated some strong candidates and indicated pathways where patterns of activity are inappropriate (c-myc, her2neu, . . .). From a clinical perspective, there are two keys issues that molecular information might powerfully

address. First prognosis has proven very difficult, it is still not possible to identify those patients who will relapse in the future and the mechanism of this relapse remains to be elucidated. In addition, arising from surgical resection, the therapeutic options are poor. Endocrine therapy, in particular has been unrewarding. The identification of aberrant signaling in granulosa cell-specific pathways could provide existing targets for the development of novel relatively specific therapeutic agents. Two experiences could be reported, one with Vorinostat (HDAC inhibitor) with excellent PR for patient with granulosa tumour and hyperexpression of EGFR 1 to 4 in juvenile granulosa tumour [23].

Follow up

Two serum markers seem to be useful as indicators of relapse: oestradiol for secretory tumours [24] and inhibin, a peptide hormone secreted by granulosa cells. The measurement of serum inhibin levels has proven to be powerful and clinically useful predictor of impending relapse [25].

Because the risk of breast cancer in these patients is not negligible, especially those with the juvenile form, clinical monitoring and regular mammograms should be performed [20].

Sertoli–Leydig cell tumours

Abstract

Sertoli–Leydig cell tumours represent 0.2% of all ovarian tumours. They belong to the group of sex-cord (Sertoli (nurse) cell)–stroma (Leydig (interstitial) cell) tumours and contain variable amounts of Sertolian and Leydigian elements. They are mostly benign, but about 20% relapse or generate metastases and can be fatal. Familial forms have often been described. Their frequency peaks in 25-year-old women. The majority of patients present with non-specific symptoms, such as an abdominal mass, pain, menstrual disorders and 50% have signs of virilisation. Surgery is the most important therapeutic modality; excision of all lesions present is the basis of treatment, but conservative surgery can often be performed at early stages. Several chemotherapy protocols have been used to treat Sertoli–Leydig tumours and complete responses have been obtained with vincristine, adriamycin and cyclophosphamide (VAC) and bleomycin, vincristine–cisplatin, adriamycin, cyclophosphamide (BV–CAP) regimens. Patients presenting signs of virilisation, i.e. those with a secretory tumour, can have their hormone (dehydroepiandrosterone (DHEA)-sulfate, estrogen, 17-hydroxyprogesterone, and cortisol) levels tested at the time of diagnosis.

Definition

Sertoli–Leydig cell tumours belong to the group of sex cord–stroma tumours. These tumours are derived from mesenchyme and sex cords which regroup histologically all the embryonic phases of testicular development: from a diffuse stromal and undifferentiated cord appearance to well-differentiated Sertoli tubes.

The majority of these tumours are benign, but around 20% relapse or give rise to metastases that can be fatal. Familial forms have been described frequently and should be sought [26]. These tumours contain variable proportions of Sertolian and Leydigian elements. Tumours with only a Sertolian component (Sertoli tumours) belong to the benign group. Tumours containing both types of components are classified into three groups as a function of the more-or-less differentiated character of the two constituents: (1) benign differentiated forms (androgenic, secretory in 60% of the cases); (2) intermediate differentiation (immature Sertoli cells); and (3) poorly differentiated forms (sarcomatoid or retiform). It is possible to see heterogeneous elements in the forms with poor or intermediate differentiation (primarily epithelial or mesenchymatous).

Frequency

These tumours represent 0.2% of ovarian tumours.

Clinical description

These tumours occur most frequently in 25-year-old women. The majority of patients present with non-specific symptoms, such as an abdominal mass, pain, menstrual disorders, and 50% have signs of virilescence [14]. Three clinical signs are highly evocative of the disease: amenorrhea, masculine voice and hirsutism associated with hypertrophy of the clitoris. Very rarely, these tumours can secrete oestrogens, which sometimes lead to precocious puberty.

Disease progression

Malignant Sertoli–Leydig tumours tend to relapse early (2–3 years). The prognostic factors include stage, histological grade (differentiation), tumour rupture and the presence of heterologous mesenchymatous constituents. The number of mitoses is a potential prognostic factor but seems to be associated with the histological grade of the tumour [26].

Management

Surgery

The comment made concerning granulosa cell tumours applies here as well. Surgery is essential but no precise recommendations can be given concerning its modalities: excision of all the lesions present remains the basic treatment. Conservative surgery to allow a future pregnancy is often possible for early stage tumours. Otherwise, it is reasonable to perform a total hysterectomy with bilateral annexectomy [18].

For young women who can be offered conservative surgery, uterine curettage must be performed before surgery [20]. Reintervention is recommended for relapses.

Radiotherapy

No data are available on the effect of radiation therapy on Sertoli–Leydig cell tumours. Although several reports indicated a certain radiosensitivity of these tumours, the associated toxicity was more severe than that of chemotherapy [26].

Chemotherapy

Several chemotherapy regimens have been used to treat Sertoli–Leydig cell tumours: alkylating agents, adriamycin, CAP (cisplatin, adriamycin and cyclophosphamide), PVB (cisplatin, vinblastine and bleomycin). In the majority of cases, the effect could not be evaluated. Partial responses of short duration have been observed and survival appeared not to be or only slightly modified [26]. Complete responses have been described for the combination of VAC and BV–CAP [27].

Follow up

Patients presenting with signs of virilisation, *i.e*. those who had developed a secretory tumour, can benefit from dosaging of hormone (dehydroepiandrosterone (DHEA)-sulfate, oestrogen, 17-hydroxyprogesterone, and cortisol) levels at the time of diagnosis. This testing can exclude adrenal abnormalities, and monitor the efficacy of treatment and post-surgical follow-up.

Gynandroblastomas

Abstract

Gynandroblastomas are extremely rare tumours that represent less than 1% of sex-cord tumours and are probably derived from undifferentiated mesenchyme. This origin would explain their ‘bisexual’ potential. These tumours contain variable but high proportions of granulosa cells and Sertoli (sex-cord, nurse)–Leydig (interstitial stroma) cells. Because of the androgenic stimulation, signs of virilescence generally predominate over oestrogenic effects.

In the majority of cases, these tumours are benign and only adapted surgery is recommended. However, certain malignant tumours have been described in the literature and they are usually large tumours, 7–10 cm in diameter, developing in women 30–50 years old. Endometrial hyperplasia is often associated and should be sought.

Therapy is the same at that for granulosa cell tumours, particularly those concerning surgery. Chemotherapy can be prescribed for tumours with a pejorative prognosis or relapses.

Steroid-producing (thecal) cell tumours, not further specified

Abstract

Thecal cell tumours, not further specified, belong to the group of sex-cord (Sertoli (nurse) cell)–stroma (Leydig (interstitial) cell) tumours and have malignant and thus metastatic potential. Clinically, they can be accompanied by signs of virilescence or hyperoestrogenic manifestations.

The stage, patient’s age, size of the tumour, presence of necrosis, nuclear atypia and the number of mitoses has been reported to have an impact on the prognosis of the disease.

Therapy is the same as that recommended for granulosa cell tumours, especially concerning surgery. Chemotherapy can be prescribed for patients with poor prognoses and those with relapses.

Conclusions

Since the 1980s, reports of patients diagnosed with stromal sex cord tumours of the ovary are retrospective analyses that span over periods of more than 10 years and include less than 300 patients [15,28–34]. Most of these published studies have combined most or all SCT subtypes, so the recommendations for treating specified tumours have been based on limited data. Most data have been gathered from patients with adult granulosa cell tumours, but when other tumour types have been encountered they usually have been treated similarly. Patients in these reports often have had different surgical procedures, even for the same stage of disease, different chemotherapy regimens in first line therapy and even more in second line therapy, and because the 10 year survival rate is rather high, interpretation of such data is hazardous. Another

reason for the difficulty is that many of these tumours are clinically indolent; so long term follow-up is required to interpret outcomes data accurately. Indeed, because the number of events (relapse or death) at 10 years is small and the patients are young at the age of diagnosis, the rate of patients lost to follow-up is important and alters the significance of statistical analysis.

Accordingly, the need for prospective data allowing for reproducible research work was important. Unfortunately, because these ovarian tumours are rare, conventional single institution clinical trials appear unsuited. Besides, beyond the need for firm clinical data on prognosis and management, physicians need rapid answers to the question they are faced with when dealing with these patients, especially when taking in account rather good prognosis and the problems of preserving fertility in these young patients.

In 2002 a French language website was created in order to inform patients and their families and keep an update of scientific and bibliographic knowledge of rare tumours of the ovary (www.ovaire-rare.org). Because these tumours are rare, a professional dedicated website was created, allowing physicians to ask for advice regarding the surgical and medical management of these patients through a discussion forum on the internet. This forum is open to all physicians who take charge of this neoplasm's both to ask for and to give advice. Clinical research programmes, as well as information for patients and families, are developed in the same time. One of the aims of the work with health professionals was to standardise the management of non-epithelial ovarian tumours all along the different stages of the disease and in doing so accumulate clinical information on the natural history and prognosis of these tumours. Consequently, an online discussion forum was created, associated with a clinical trial on which patients who met inclusion criteria could be included online.

Perspectives

Between March 2002 and December 2006, 98 patients have been included in the programme. The inclusion rate, which seems to be improving with time, resembles that of other clinical trials. Clinical data is available for 40 of the 98 presently included patients. Median age at diagnosis is 36, stage distribution is as follow: 60% of stage I, 10% of stage II, 20% of stage III and 10% of stage IV disease. The main sites for metastasis are the liver and the lung. The median tumour size is 11 cm and the most frequent histological types are sex cord-stromal tumours with 40% of granulosa cell tumours and dysgerminoma with 20%.

Interestingly, the centralised review of tumour samples by expert pathologists changed the diagnosis in 38% of patients (9/24). The diagnostic modification involved the histological type in 7/24 patients (29%) and sub-type or grade in 2/24 patients (8%) [35]. Modification of diagnosis concerns unclassified sex cords 'becoming' synovialosarcoma, juvenile granulosa tumour translate in dysgerminoma, granulosa adult in fibrosarcoma [2] or in Sertoli tumour [1] and one Sertoli Leydig in fibrothecoma.

A website with online information, bibliography and a discussion forum dedicated to these tumours appeared adapted to the peculiar problems we had to deal with. The rate of study entry after 4 years seems to confirm the website's ability to help clinical research. Still, the numbers of cases discussed on the forum being inferior to the number of patients included in the clinical trial results in the question arising of the actual value of 'service' that is rendered to clinicians. Nevertheless, this experience allows both patients and physicians to have rapid access to information regarding these rare neoplasms, and in the same time enables progression of clinical research and centralised accumulation of data with the aim to improve the management of these young patients.

Conflict of interest statement

None declared.

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