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Review

Malignant mixed mesodermal tumours: biology and clinical aspects

C. Gourley[a,*], A. Al-Nafussi[b], M. Abdulkader[b], J.F. Smyth[a], H. Gabra[a]

[a]*ICRF Medical Oncology Unit, MRC Building, Western General Hospital, Edinburgh EH4 2XU, USA*
[b]*Department of Pathology, University of Edinburgh, Bristo Square, Edinburgh, UK*

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Abstract

Mixed mesodermal tumours (MMTs) are relatively rare gynaecological tumours that have been poorly studied in clinical and molecular terms. They are chemosensitive (at least initially), although ultimately they have a poor prognosis. The biology of the tumour is fascinating in view of its composition of both epithelial and mesenchymal entities. We review herein the literature on the clinical and biological aspects of this malignancy.

Keywords: Cancer; Mixed malignant mullerian tumour; Mixed malignant mesodermal tumour; Carcinosarcoma; Sarcomatoid carcinoma

1. Introduction

Malignant mixed mesodermal tumours (MMMTs), also termed carcinosarcomas, sarcomatoid carcinomas or malignant mixed Müllerian tumours, are rare tumours of gynaecological origin, which typically present in elderly postmenopausal women. They are chemosensitive initially, but relapse quickly and have a poor prognosis. They can originate in the ovaries, uterus, fallopian tubes, vagina, peritoneum or (rarely) at extragenital sites.

Histologically, MMMTs consist of both a carcinomatous and a sarcomatous component. There has been considerable debate as to the pathogenesis of these entities, but immunological and molecular studies have suggested that both malignant elements originate from a common stem cell (the combination theory) as opposed to two distinct malignant cell populations of different origin (the collision theory). Approximately 50% of MMMTs are regarded as 'heterologous' due to the presence of a stromal component containing mesenchymal tissue not found at the normal primary site. Previously, it was felt that heterologous MMMTs carried a worse prognosis, but recent evidence suggests this histological feature does not significantly affect prognosis.

Long-term survival is an unlikely prospect, but is mainly determined by curative primary surgery. There appears to be a role for chemotherapy as palliation in the setting of advanced disease, although its role in the adjuvant setting has not been clarified within the context of randomised controlled trials.

2. Epidemiology

MMMTs are known to arise from the uterine corpus [1–3], uterine cervix [4], ovaries [1,5–7], fallopian tubes [8–10], vagina [11], peritoneum [12–14], as well as very rarely at extragenital sites [15,16]. They are rare, comprising 2% of all gynaecological malignancies [2]. MMMTs in various series have been found to account for 2–3% of all uterine malignancies [3,17] and approximately 1% of all ovarian malignancies [6]. The vast majority of these cases occur in elderly, postmenopausal women, although they can affect younger patients.

Suggested predisposing factors for MMMTs include previous pelvic radiotherapy [1,2,18], nulliparity [2], diabetes [3,19], obesity [3,19] and non-contraceptive oestrogens [20]. Uterine MMMT patients who have been previously irradiated for other malignancies also have a worse prognosis, perhaps due to the surgical difficulties encountered [21–23], or because further radiotherapy options are limited. Cases of tamoxifen-associated uterine MMMTs have been clearly documented [24–27].

* Corresponding author. Tel.: +44-131-777-3539; fax: +44-131-777-3520.
E-mail address: charles.gourley@cancer.org.uk (C. Gourley).

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3. Clinical presentation

Ovarian MMMTs present in a similar way to carcinomas of the ovary with abdominal distension, pain, nausea, vomiting and weight loss. In some series, the pattern of spread was found to be similar to epithelial lesions with early serosal and peritoneal dissemination [6]. Furthermore, the clinical behaviour of uterine MMMT is thought to more closely resemble high-grade endometrial carcinoma rather than uterine sarcoma [4]. In general, the behaviour of MMMTs is more aggressive than the equivalent epithelial lesion with figures for 1-year survival in ovarian MMMT of between 23 and 63% [5,28,29] (depending on the particular cohort examined) and figures for 5-year survival in uterine MMMT varying between 18 and 42% [21,30–32]. In one series, the 2-year survival in uterine MMMT was 50% for stage I/II disease, but 0% for stage III/IV disease [2]. The aggressive nature of the malignancy is demonstrated by a series of uterine MMMT patients, of whom a high proportion were stage I (59%), yet the 5-year survival was only 38%, with $>90\%$ of recurrences and $>80\%$ of metastases occurring within the first 2 years [33].

4. Pathogenesis

Since MMMTs consist of both epithelial and mesenchymal elements, there has been considerable interest in the mechanism by which they arise. The collision (or biclonal) theory which proposes two distinct malignant cell populations arising separately to form the tumour had some early support [1,3], but most evidence now supports the combination (or monoclonal) theory [34–46], including some recent immunological [34,39,41,44–46] and molecular data [42,43] which points towards a common bipotential malignant 'stem cell' as the origin of both tissue types in mixed mullerian tumours. It may be that MMMTs arise from Mullerian epithelium with subsequent divergent differentiation or metaplasia to sarcomatous elements [34–38] (the conversion hypothesis).

Most investigators have found the initial metastases of uterine MMMTs to be purely carcinomatous, less frequently mixed and rarely purely sarcomatous [3,40,47]. Silverberg and colleagues (1990) [40] noted that lymph node metastases occurred with about the same frequency encountered in poorly differentiated carcinomas and concluded that this suggested the carcinomatous element was the driving source. Deligdisch and colleagues (1988) [34] looked at 10 extra-uterine MMMTs and found that the metastatic lesions at initial surgery were predominantly epithelial, but that subsequent recurrences were predominantly mesenchymal, raising the possibility that the malignant 'stem cell' differentiates first into the carcinomatous component then into the sarcomatous component. This may explain why the findings of Muntz and colleagues [7] contradict others above by suggesting that in ovarian MMMT the metastatic deposits consist mainly of stromal elements. Sreenan and Hart [48] evaluated the cellular composition of 62 metastases from 29 MMMTs (51 diagnosed concurrently with the primary tumour and 11 diagnosed 2–26 months after the initial treatment). Carcinoma only was found in 43 (69%), carcinoma and sarcoma in 15 (24%) and sarcoma only in 4 (6%). Of 35 lymph node metastases, 34 were carcinoma alone. Of 19 intraperitoneal metastases, 14 consisted of both carcinoma and sarcoma and five consisted of carcinoma alone. Of four distant organ metastases, those to the liver and breast (1 case of each) were carcinoma alone and those to the bone marrow and brain (1 case of each) were sarcoma alone. These findings suggest a dominant role for the epithelial component and a role for the site of metastasis in determining the cellular composition of the metastasising cells (or indeed the converse). There was also a difference in the cellular composition of the metastases diagnosed concurrently with the primary compared with those diagnosed later suggesting the metastasising cells may be influenced by temporal factors.

5. Molecular/cell biology aspects of MMMTs

Some studies have looked at MMMTs in isolation, but many have included one or two cases as part of ovarian or uterine series and felt them worthy of mention as, unsurprisingly, the molecular findings have differed. Many of the molecular/cell biology studies have been performed to answer the question of whether MMMTs are of monoclonal or biclonal origin and these are mentioned elsewhere in the text (see 'Pathogenesis' above).

Abeln and colleagues [43] found loss of heterozygosity in 5 out of 6 MMMT cases using 74 polymorphic microsatellite markers. The most frequently involved chromosomes were 17p, 17q, 11q, 15q and 21q. Identical alleles were lost in the epithelial and mesenchymal cells (suggesting a monoclonal origin to the tumour). They also identified *TP53* mutations in five out of the six tumours.

Soong and colleagues [49] found nuclear p53 overexpression in 12 out of 24 MMMTs and *TP53* mutations by single-strand conformation polymorphism (SSCP) of exons 5–8 in 11 out of 24 tumours.

The authors suggest that, unlike in other tumours, *TP53* gene alteration does not appear to be of prognostic importance. In a study looking at murine double minute 2 (MDM2) expression in relation to p53 expression [50], the only ovarian line with positive immuno-

cytochemistry for MDM2 was a MMMT line. A possible interpretation of this is that the presence of a protein that can sequester wild-type p53 in the MMMT line, and not in the ovarian adenocarcinoma lines, is associated with the presence of the sarcomatous elements in the MMMT.

Jeffers and colleagues [51] found overexpression of c-myc in nine out of nine MMMTs. In three MMMT cell lines (with rhabdomyosarcoma as the mesenchymal component), Emoto and colleagues [52] found 4- to 8-fold amplification of the *c-myc* gene without any amplification of the *MYCN* gene.

There is also evidence of altered methylation affecting gene expression in MMMT. Hashimoto and colleagues [53] found a 6.3-fold upregulation of *H19* (with biallelic expression) in a uterine MMMT compared with normal myometrium. The *H19* 5′ promoter region was hypomethylated in the tumour, but hemimethylated in the normal myometrium. It was suggested that overexpression of *H19* may play a significant role in the tumorigenesis of MMMT and that it may have tumour promoting activity, in addition to its tumour suppressing activity, probably depending on the tissue type and local milieu.

In terms of cell biology, a MMMT cell line derived from a nude mouse heterotransplant was successfully maintained in culture for many months [54], still exhibiting a tumorigenic phenotype and with flow cytometry data suggesting that both epithelial and heterologous portions of the tumour were still distinguishable.

More recently, Becker and colleagues [55] showed expression of both epithelial antigens (cytokeratin, epithelial membrane antigen and carcinoma antigen TAG-72) and mesenchymal moieties, such as vimentin and desmin (although aberrant expression of filaments is quite common and therefore not a particularly good distinguishing factor) in the LN1 cell line derived from a MMMT. Karyotypically, this cell line had a triploid pattern with multiple chromosome abnormalities and constitutively expresses *c-ras*, *c-erb B2* and *TP53* both at the mRNA and protein level (p21 H-ras, p21 K-ras, p185erB2 and mutant p53 protein).

Firm conclusions about the molecular aspects of MMMT are difficult to draw because of the paucity of studies that have looked specifically at MMMT rather than included them in larger series of other gynaecological malignancies. However, it does appear that c-myc overexpression is frequent, if not ubiquitous, that *TP53* mutations are common (although like in other tumours they may occur fairly far down the road to oncogenesis, conferring a selective growth advantage on the tumour cells that acquire them) and that demethylation may have a role in tumorigenesis of MMMT. Nevertheless, further work is required on the basic biology of this rare and unusual tumour type.

6. Prognostic factors

Many studies have retrospectively analysed series of MMMT cases to identify which clinical or pathological features might influence outcome. The resounding message from these studies is that in either uterine or ovarian MMMT the most important (and in many cases the only) prognostic factor is the stage of disease at presentation.

Chang and colleagues [5] in a series of 37 patients showed that the favourable feature of early International Federation of Gynecology and Obstetrics (FIGO) stage in ovarian MMMT was the only independent prognostic factor for survival. Histology of the tumour (i.e. homologous or heterologous sarcomatous components; grade/type/percentage of epithelial components) had no significant impact on survival. In addition, in MMMT of ovarian origin, Barakat and colleagues [56] found a significant survival advantage for stage I/II (104.8 months) compared with stage III/IV (9.5 months) ($p = 0.01$). Sood and colleagues [57] also showed early stage to be a significant predictor of improved survival in ovarian MMMT ($p = 0.04$, although 15% of patients had pure sarcomas). Stage was found to be important ($P < 0.001$) in a small retrospective series reported by Muntz and colleagues [7], as was the feasibility of cytoreductive surgery (in stage III/IV ovarian MMMT the 2-year survival was 52% for optimal cytoreduction versus 14% for suboptimal cytoreduction; $P = 0.03$). In a more recent Swedish study [58], the most important predictors for survival in ovarian MMMT in a multivariate analysis were stage ($p < 0.08$, histological type (homologous versus heterologous, $p < 0.05$) and type of chemotherapy (cisplatin, doxorubicin and melphalan containing regimens were more favourable, $p < 0.08$).

In uterine MMMT, some studies have shown stage to be the only important prognostic factor [59,60]. In 21 cases of uterine MMMT, To and Ngan [2] found that all of the long-term survivors had superficial myometrial invasion only. In tumours without extra-uterine spread, the depth of myometrial invasion has been shown to be an important prognostic factor [21,22,61]. Tumours consisting only of a polyp have the best prognosis and this is usually compatible with long-term survival [21,62,63]. The degree of myometrial invasion, vascular permeation, cervical and lymph node involvement all appear to be interdependent factors. Since stage of disease is so critical as regards outcome, it is worth remembering that staging is often incomplete unless dissection of retroperitoneal lymph nodes is undertaken because studies [3,4] have shown that 45% of patients with apparent stage I disease have positive retroperitoneal lymph nodes. In a more recent study of clinicopathological variables associated with extra-uterine disease, recurrence and survival in patients with surgically-evaluated uterine MMMT [61], depth of myometrial invasion and

lymph-vascular space invasion were associated with extra-uterine diseases ($p < 0.05$). Factors associated with recurrence and survival included depth of myometrial invasion, lymph-vascular space invasion, adnexal and serosal involvement, positive cytology and lymph node metastases (in all cases $p < 0.05$).

Originally, it had been suggested that the presence of heterologous sarcomatous elements was an adverse prognostic factor and although some studies [57,58,64] agree with this, in a large number of studies [4,5,7,21,31,32,35,40,46,65,66] this feature was not found to be a significant prognostic factor.

Controversy regarding the importance of the histology of the epithelial component has been generated with some studies finding this an important prognostic factor [7,13,40,67], whilst other studies have not validated this finding [4,5].

Interestingly, one study [57] showed that 93% of ovarian sarcoma patients (85% of whom had MMMT) had an elevated CA125 level preoperatively; a level <75 U/ml preoperatively was associated with a better survival ($P = 0.01$).

A percentage of uterine MMMTs express ER/PR in the epithelial or stromal component or both and there is a suggestion that those who do have a better prognosis [68]. Sex hormones have previously been proposed as having a role in endometrial adenocarcinomas and other gynaecological malignancies [69–72].

7. Treatment options

It is reasonable to assume that radical surgery represents the best prospect for long-term survival from MMMT regardless of the primary site, particularly for early stage disease. Most patients, however, present late with pelvi-peritoneal dissemination [5,6] and few of these patients survive more than 2 years [56,73]. In ovarian MMMT, surgery aims for optimal cytoreduction [74] (as is the case for epithelial lesions) but, because of the rarity of the lesion, it is difficult to draw definitive conclusions regarding treatment approaches since randomised trials are difficult to perform. The case for surgery, radiotherapy and chemotherapy in the treatment of MMMT will be considered in turn based on available data. For all mixed mesodermal tumours, multimodality therapy should be considered.

7.1. Surgery

Surgical management aims to treat both the epithelial and sarcomatous components of the tumour. Some studies do not show any advantage in optimal cytoreduction [56,75], but some of these series are small [56] and in others many different post-operative treatment regimes were used [75]. Anderson and colleagues [29] reported on one small series in ovarian MMMT which showed a dramatic difference in survival depending on the degree of cytoreduction, but stage was not taken into account. In a study of platinum-based chemotherapy in ovarian MMMT, Bicher and colleagues [6] looked at the surgical response (by second-look laparotomy) in a cohort of 9 of these patients; the 5 patients who had a 'surgical CR' had all been debulked to less than 2 cm of residual disease. In a study of 'primary ovarian sarcoma' [57], where 85% of the patients had MMMT (the others having pure sarcoma), optimal cytoreduction significantly predicted for increased survival ($P < 0.001$), even in stage III/IV disease ($P < 0.001$). Other studies [7] have suggested a significant survival advantage associated with optimal cytoreduction in women with stage III/IV ovarian disease. Although there is less data on the role of debulking surgery in uterine MMMT, it is reasonable to suggest that early disease can be cured by surgery. Optimal treatment of more advanced disease requires surgery and radiotherapy (see below) ±chemotherapy. Surgery would therefore appear to be the first treatment option that should be considered in all uterine MMMT patients who are fit for this. The histological similarity of all MMMTs regardless of the primary sites (they all derive from the primary or secondary Mullerian system [76]) suggests that it might be possible to draw tentative conclusions about the response to a treatment modality of MMMTs originating at one site to MMMTs at different sites of origin.

As regards lymph node dissection, it does improve staging accuracy considerably [61] and was used in the uterine MMMT series [77] in which the patients treated with multimodality therapy achieved an exceptional survival, but whether lymph node dissection itself improves patient outcome is something that would require investigation in the context of a randomised controlled trial.

7.2. Radiotherapy

Radiotherapy aims to treat both the epithelial and sarcomatous components of the tumour. The epithelial component may be expected to respond promptly, but taking into account the cell loss factor it is conceivable that there would be a late response in the sarcomatous component. Whilst most surgical series have looked at ovarian MMMTs, most of the data about the role of radiotherapy for MMMTs is for uterine primaries (since radiotherapy has proven to be a more useful treatment modality in adenocarcinomas of the uterus than in those of the ovary). Hornback et al [78] observed a decrease in pelvic recurrence in non-leiomyosarcomatous uterine sarcomas (87% of this study group being MMMTs) following radiotherapy, although the analysis was retrospective, with varying radiotherapy doses and techni-

ques. Perez et al [79] found a decrease in pelvic recurrence in uterine MMMT following 60 Gy of radiotherapy compared with 50 Gy, but this did not reach statistical significance. Larson and colleagues [80], again looking at uterine MMMT obtained better control with combined brachytherapy and external beam radiotherapy compared with each modality alone. Even in early disease there are suggestions that radiotherapy can be of benefit. Salazar and colleagues [81] retrospectively analysed uterine sarcoma patients in a tumour registry and found that all 6 patients with stage I uterine MMMT treated with surgery alone progressed, whereas this only occurred in 6 out of 12 patients treated with surgery and radiotherapy. Knocke and colleagues [82] compared the 5-year actuarial overall survival, disease-specific survival, local control and distant control for 50 patients receiving surgery and adjuvant radiotherapy for uterine MMMT with historical controls who received surgery alone. These data suggested that adjuvant radiotherapy improved local control and disease-specific survival. The role of adjuvant radiotherapy in stage I/II high-grade uterine sarcoma (including MMMT) is currently being evaluated within a randomised phase III trial (compared with observation, EORTC 55874). In addition, the Gynecologic Oncology Group (GOG) are currently recruiting patients with MMMT of the uterus into a randomised multicentre study (GOG 150) comparing the survival, progression-free interval and failure patterns when treatment is with whole abdominal radiotherapy compared with treatment with ifosfamide and cisplatin. The study also aims to determine and compare the incidence and type of acute and late adverse events observed with these treatment regimens in this patient population.

7.3. Chemotherapy

Chemotherapy aims to treat to varying degrees (depending on regimen) both components of the tumour. Platinum-based therapy is aimed mainly at the epithelial component whilst anthracycline and alkylating agent therapy are aimed mainly at the sarcomatous element, although the latter, in particular, could have considerable effect on the carcinomatous component.

The rarity of MMMTs has meant that the chemotherapy data consists mainly of retrospective analyses of series of patients. This makes it difficult to control for confounding factors such as age, stage, grade, histological subtype, size of residual tumour, as well as changes in medical and surgical techniques that occur over the long period that it takes to accumulate such cases [6]. While some studies have claimed to investigate the adjuvant setting [83,84] (and suggested some survival benefit to chemotherapy in addition to initial surgery), the rarity of this lesion has meant that most series have looked at all the patients and considered the response rate to a particular regime, regardless of stage (Table 1).

Some agents have been disappointing, such as etoposide which was found to have only a 6% response rate in uterine MMMT [85] (although in the setting of advanced or recurrent disease), and doxorubicin which as a single agent had little effect when used as first-line therapy in 10 ovarian MMMT patients [86].

As far as single agent therapy is concerned, ifosfamide appears to be active with a 32% response rate having been reported in first-line treatment for advanced or recurrent uterine MMMT [87]. Similarly, intravenous (i.v.) cyclophosphamide has provided two prolonged complete responses (CRs) and one partial response (PR) in a group of only 3 patients treated by Prendiville and colleagues [88]. In a recent study of paclitaxel in patients with persistent or recurrent uterine MMMT who had failed other treatments, Curtin and colleagues [89] found a response rate of 18%. Several studies suggest that single agent platinum may be effective. Gershenson and colleagues [76] achieved a 42% response rate to single-agent cisplatin in uterine MMMT, but the median progression-free survival was only 4–5 months. Chang and colleagues [5] showed a 35% response rate to single-agent platinum (either in the form of cisplatin or carboplatin) and a 29% response rate to platinum-based chemotherapy (including combinations) in patients with residual ovarian MMMT postsurgery. The median duration of response in all of the patients in this series was 331 days, but some patients survived more than 5 years. Bicher and colleagues [6] treated 36 ovarian MMMT patients with platinum-containing chemotherapy (cisplatin, doxorubicin and cyclophosphamide in 16; cisplatin and ifosfamide in 5; cisplatin and cyclophosphamide in 4; cisplatin and doxorubicin in 3; carboplatin in 3 and other platinum-containing regimens in 5), achieving a 44% CR rate and 25% PR rate giving an overall response rate of 69%. The median survival was only 18 months, but there was a small percentage of patients who remained disease-free. In a small series (13 patients), Plaxe and colleagues [75] showed an 85% response rate in patients with advanced ovarian MMMT treated with either cisplatin, doxorubicin and cyclophosphamide or cisplatin and cyclophosphamide, although the median survival was only 16 months. Similarly, in a small series, Andersen and colleagues [29] used cisplatin-based combination chemotherapy to treat stage III suboptimally debulked primary ovarian MMMT. Of 6 patients, 4 achieved a CR (median duration of response 13 months) and the other 2 achieved a PR (response durations 2 and 11 months). Again, although response rates are impressive, overall survival was poor. Sood et al [57] have compared chemotherapeutic regimes (although admittedly 15% of the patients had pure sarcomas and once again the study was retrospective) in 47 patients and their data suggested a significantly

Table 1
Response rate to cytotoxic agents used in MMMT

Cytotoxic agent(s)	Response rate (%)	Evaluable patients	Setting	Reference
Etoposide single agent	6	31	Advanced/recurrent uterine MMMT	[85]
Doxorubicin single agent	10	10	First-line ovarian MMMT	[86]
Ifosfamide single agent	32	28	Advanced/recurrent uterine MMMT	[87]
Cyclophosphamide single agent	100[a]	3	Ovarian MMMT	[88]
Cisplatin single agent	42	12	First- and second-line uterine MMMT	[76]
Cis/carboplatin single agent	35	17	Residual ovarian MMMT postsurgery	[5]
Platinum-containing chemotherapy (various)	69	16	First-line ovarian MMMT	[6]
Cisplatinum/adriamycin/cyclophosphamide combinations	85	13	Postoperative in stage III or IV ovarian MMMT	[75]
Cisplatin-based combination chemotherapy	100[b]	6	Sub-optimally debulked stage III ovarian MMMT	[29]
Ifosfamide and cisplatin combination	54	92	Advanced, persistent or recurrent uterine MMMT	[91]
Cisplatin single agent	18	18	Second-line uterine MMMT	[92]
Ifosfamide single agent	18	28	Recurrent ovarian MMMT (already had platinum)	[93]
Hydroxyurea, dacarbazine and etoposide	15	32	Advanced/recurrent uterine MMMT	[94]
Paclitaxel single agent	18	44	Advanced/recurrent uterine MMMT	[89]

MMMT, malignant mixed mesodermal tumours.
[a] Extremely small patient group: 3 patients only.
[b] Very small patient group: 6 patients only.

increased response if the chemotherapy was platinum-based ($P=0.008$), as well as a significant survival advantage ($P=0.03$). In ovarian MMMT patients, Carlson and colleagues [90] demonstrated a 42% response rate with vincristine, actinomycin D and cyclophosphamide, although again the one year survival in this group of patients was poor at only 33%.

In the only completed randomised trial to date, performed by the GOG, [91] 194 patients with advanced, persistent or recurrent uterine MMMT were randomised to ifosfamide alone or ifosfamide plus cisplatin. Although there was a significant increase in the response rate with the combination therapy, there was only a slight prolongation of progression-free survival and no significant increase in overall survival. There was significantly increased toxicity in the combination arm, requiring a 20% reduction in the dose of both drugs early in the study.

In the second-line setting, Thigpen and colleagues [92] showed a 18% response rate to cisplatin in uterine MMMT. In addition, Sutton and colleagues [93] report an 18% response rate to ifosfamide in recurrent ovarian MMMT in patients who had already received platinum. In a phase II study of hydroxyurea, dacarbazine and etoposide performed in patients with advanced or recurrent uterine MMMT, a modest (15%) response rate was demonstrated [94]. Although the epithelial component appears to be solely responsible for most mestastases [48] and there is a temporal difference in the cellular constituents of metastases, no studies have so far looked at the cellular constituents of metastases after first-line chemotherapy. This is an interesting question that could be addressed if tissue could be obtained in a relatively non-invasive fashion, perhaps with a view to tailoring second-line therapy.

As regards the newer agents, there have been case reports of excellent responses (e.g. paclitaxel in combination with cisplatin [95,96]), but higher quality evidence is lacking at this time. Currently, the GOG are conducting a randomised multicentre study (GOG 161) aimed at determining whether addition of paclitaxel to ifosfamide improves the length of survival, progression-free interval and response rate when compared with ifosfamide alone in patients with advanced, refractory or recurrent MMMT of the uterus.

The message from most of the reported series is the same; MMMT is a chemosensitive tumour, but the duration of response is often poor and the ultimate outlook for the majority of patients is bleak. In most series, however, there are a small percentage of long-term survivors, even when presenting with advanced disease. There are also case reports of exceptional survival following chemotherapy for advanced or residual disease [97,98] and of pathological complete response to cytotoxic treatment [99]. These features of MMMT reinforce the search for an optimal cytotoxic regimen for adjuvant treatment or for the treatment of advanced disease. This can only be done in the context of multicentre randomised controlled trials.

In view of the fact that data from a meta-analysis suggests carboplatin and cisplatin are comparable in epithelial ovarian carcinoma and that 75 mg/m^2 of doxorubicin is the 'gold standard' for soft-tissue sarcoma (as well as the Bonnadonna breast cancer experience), it would be interesting to conduct a randomised phase II trial of up-front versus delayed sequential full-dose doxorubicin then full-dose carboplatin. This would be supported by the response rate data from the above small series for doxorubicin and platinum-based combination therapies and from the exceptional results in a

series of patients treated with multimodality therapy by Manolitsas and colleagues [77] (see below), perhaps without the adverse toxicity profiles associated with cisplatin/ifosfamide combination chemotherapy.

7.4. Multimodality therapy

In a series of 38 patients with clinical stage I or II uterine MMMT, Manolitas and colleagues [77] showed a 95% overall survival rate (90% disease-free survival) with a mean follow-up of 59 months when uterine MMMT patients were treated with a protocol of laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node exploration (±dissection), tailored radiotherapy and chemotherapy consisting of cisplatin/carboplatinum and an anthracycline. In contrast, the patients treated in the same institutions who did not receive the full multimodality treatment for their stage I or II uterine MMMT (for a variety of reasons, e.g. choosing to decline chemotherapy or radiotherapy or being of too poor performance status for chemotherapy) had an overall survival of 47%. Despite the obvious problems with comparing two groups of this type, the survival figures for the multimodality group are exceptional and should at the very least stimulate a full investigation of this treatment protocol in a prospective randomised controlled trial.

8. Discussion

MMMTs are rare tumours and single academic institutions therefore only have a limited exposure to them. The lack of prospective controlled trials makes it difficult to validate any of the treatment modalities. Early-stage patients whose tumours can be fully resected are probably the only curable group. Many patients with this disease are elderly and frail. The only factor that has been consistently shown to affect prognosis is the stage of the tumour at presentation. Other pathological factors such as type of sarcomatous elements, grade, type or extent of epithelial components have not been shown to consistently affect prognosis and therefore should not be used for making treatment decisions.

According to the limited current evidence, all patients fit for surgery should be optimally debulked and patients with uterine MMMT should be considered for radiotherapy. The role of adjuvant radiotherapy is currently being considered within the phase III EORTC55874 protocol. As regards chemotherapy, many small series have suggested that this is a chemosensitive tumour. Single agent platinum is the most tried and has a response rate as high as 42%. Ifosfamide and cyclophosphamide also show promise as single agent therapy [87,88] and very high response rates (85%) have been demonstrated for cisplatin, doxorubicin and cyclophosphamide combination regimens.

Unfortunately, in most studies, the duration of response was short and long-term survivors were only found in stage I/II patients. Multicentre randomised controlled trials are required to address whether or not chemotherapy is beneficial as a component of radical therapy, and this could ethically be conducted as a randomised study against no treatment. Prospective detailed analysis of molecular markers may reveal hitherto unidentified prognostic and predictive factors to guide patient counselling and individual treatment decisions. It is likely that minor to moderate benefit will be achieved with chemotherapy and since the majority of patients will be old and frail, it could be argued that an exploration of chemotherapy combination and dose intensity may be inappropriate. However, in view of the potential chemosensitivity of the tumour and the chance of survival, even in a small percentage of advanced cases, younger, fitter patients should be considered for chemotherapy within randomised controlled trials. Further research is required to identify targets for biotherapy and profitable areas are likely to include signal transduction/hormonal pathways, angiogenesis and cytokine therapy.

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