22
DIFFERENCES IN MANAGEMENT AND TREATMENT: A CRITICAL APPRAISAL FROM A UK PERSPECTIVE

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22.1 INTRODUCTION

Gestational trophoblastic disease (GTD) is such a rare condition, with acknowledged geographical and cultural differences in behavior, that it is not surprising that management and treatment philosophies should vary across the world. In developed health care systems:

- accurate registration and follow-up data are usually available, and often reported on a formal basis;
- clinical management (diagnosis, staging and treatment) is usually undertaken by health professionals skilled in the care of these specialized conditions according to agreed local (and sometimes national) protocols;
- the disease is usually detected in 'early' stages;
- follow-up is not usually a problem.

In less developed countries, particularly in Asia, Africa, South America and the Indian subcontinent:

- population-based incidence and outcome data are less easy to come by;
- treatment is undertaken in hospitals by caring but not necessarily specialized staff, with suboptimal health care and drug resources;
- patients often present late in their disease;
- adequate follow-up is often impossible.

Differences in management between different treatment centers in the West (particularly between the USA and UK) are largely a reflection of the 'local' experience and expertise of the center, and of patient expectation and medicolegal implications. Recommendations regarding the initial management of trophoblastic disease have been issued by the Royal College of Obstetricians and Gynaecologists, UK [1] and for the disease as a whole, by the American College of Obstetricians and Gynecologists [2] and European Society of Medical Oncology [3]. Also, recently, diagnosis and management have been consensus reviewed in a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup [4].

22.2 NOMENCLATURE

Whilst there is now general agreement on the terms complete and partial hydatidiform mole the nomenclature in persistent GTD is not standardised. The terms gestational trophoblastic tumour and persistent trophoblastic disease have been used interchangably to include persistent mole, invasive mole and choriocarcinoma. In Japan when pathological material is not available a scoring system defines an entity known as 'clinical choriocarcinoma'. Many experts distinguish prognostically between metastatic and non-metastatic persistent trophoblastic disease; others prefer to look at other risk factors when making treatment decisions. The term gestational trophoblastic neoplasia (GTN) encompasses any persisting trophoblastic disease without implying presence or absence of malignancy. This term is therefore used with reference to the FIGO/WHO staging/scoring system [5].

22.3 CLINICAL PRESENTATION

The clinical presentation of molar pregnancy has changed considerably over the past two decades – excessive uterine size, anaemia, hyperemesis and metastatic disease are far less common [6,7].

In contemporary gynecological practice there is now general awareness of the protean clinical manifestations of GTN and the need to refer such cases to 'expert' centers. When such patients present to other clinicians, particularly with non-gynecological symptoms and signs (the classic examples being respiratory or central nervous system presentations), the diagnosis is often delayed, primarily because it comes a long way down the list of differential diagnoses.

However, in some countries, even where a formal or semi-formal registration system exists referral to a center may not be made – either at the request of the patient or more likely a feeling on the part of the attending physician that he or she is competent to undertake the full clinical care of that patient. There is however, a growing body of evidence suggesting that patients with rare cancers are best treated in special centers ideally with a multidisciplinary approach[8,9].

In developing countries, patients frequently present with advanced local or metastatic disease and may never be referred to expert centers – either because of the difficulties on the part of the patient in actually travelling to that center or because of the non-existence of such a center.

The UK registration, screening and treatment facility is generally regarded as the ideal model for the management of GTD; the excellent results in those patients who eventually come to treatment are a testament to the success of this surveillance scheme [10]. In other developed countries, particularly the USA, large university hospital centers have been established for treatment; these are, however, few and patients are referred from local practitioners (most often gynecologists) perhaps at presentation but also when problems start to develop, for

example with GTN resistant to treatment. In the UK such patients are rarely seen and then most often from overseas; this is a particular feature of the Charing Cross (London) center practice.

22.4 MANAGEMENT

If it is accepted that patterns of presentation vary then obviously management protocols will be adapted to take into account these local factors. There is no conclusive evidence to suggest that there are major variations in the natural history of GTD once detected, yet more patients will be treated for GTN in the USA (approximately 20%) than in the UK (less than 10%). The level of investigation undertaken depends on:

- the availability and 'up-to-dateness' of those investigations available;
- the requirements of the staging/prognostic scoring system being used;
- clinical research into new investigational methods being undertaken at the time.

The availability of sophisticated human chorionic gonadotropin (hCG) assay systems and high-technology scanning facilities has led (sometimes) in developed countries to a more intensive investigation of patients, but as yet this has not influenced clinical management protocols, most of which are based on traditional (and largely unchanged) staging/prognostic scoring systems relying broadly on clinical criteria, simple radiological tests and a satisfactory broad-spectrum hCG assay [11]. Whilst undoubtedly computed or positron emission tomography, magnetic resonance imaging scans, immunoscintigraphy and sophisticated ultrasonography give more information regarding individual patients [12], many authorities still recommend that the basic investigations should simply include clinical assessment, broad spectrum hCG assay, chest radiology and pelvic ultrasonography, and will make their decisions on treatment and/or further investigation on the basis of these evaluations [13,14]. This is certainly so for the FIGO 2000 staging/scoring system [5].

22.5 TREATMENT

Suction curettage is the preferred method of evacuation of hydatidiform mole. Medical evacuation is not recommended as this increases the likelihood of subsequent chemotherapy [15]. Opinions vary as to the role of pre-evacuation oxytocic therapy. In the UK it is recommended, where possible, that oxytocic therapy is commenced only once evacuation is complete, because of concerns over promoting dissemination of trophoblastic tissue. Second evacuation may have a role in selected cases of persistent disease [16]; this is being evaluated in a GOG trial.

Hysterectomy remains a reasonable option for fit, usually older, patients with family completed and to whom sterilization is acceptable – the risk of persistent GTD falls from 20% to below 10% [17].

Very few experts disagree on the management of locally advanced/bulky or grossly metastatic disease, proven choriocarcinoma or very high hCG. Once the diagnosis has been established (clinical/radiological evaluation, evacuation histology, hCG level) most authorities would institute chemotherapy without much delay.

For non-metastatic disease the situation is different. The criteria for starting chemotherapy vary from center to center. The place for prophylactic chemotherapy (i.e. at the time of molar evacuation) is still being debated. This would seem a valuable option for patients with high-risk complete moles in countries where clinical or technical resources are not available to monitor patients, or where patients may be non-compliant. The risk of GTN and/or metastases is reduced from about 50% to 10% [18]. In centers where facilities for treatment and follow-up are optimal, the role for prophylactic chemotherapy can be disputed:

- there is unnecessary exposure (albeit brief), to chemotherapy in over half of such patients;
- protection against GTN is incomplete;
- a false sense of security (possibly with inadequate follow-up) might be engendered.

For this reason many centers rely on a close clinical and biochemical (hCG) monitoring in all cases following adequate evacuation.

The indications for treating GTN have varied significantly, particularly between the USA and the UK (where a more conservative approach is adopted). In the USA a standard recommendation was that if hCG levels increase or plateau over a period of three or more consecutive weeks, immediate work-up and treatment for post-molar GTN are indicated. At the other end of the spectrum UK clinicians advocated a more expectant policy, and in low-risk cases we are prepared to wait up to six months following these patients with serial hCG estimations, provided the hCG is falling. It has been proposed by FIGO [5] that post hydatidiform mole trophoblastic neoplasia should be diagnosed when;

- the plateau of hCG lasts for 3 measurements over a period of 4 weeks or longer
- there is a rise of hCG on three consecutive weekly measurements over a period of two weeks or longer
- there is histologic diagnosis of choriocarcinoma
- the hCG level remains elevated for 6 months or longer

More recently it has been suggested that the latter two categories are no longer absolute indications for commencing chemotherapy [19,20].

At the Sheffield center we treat only 6% of our registered patients [21], compared with 8% at Charing Cross and approximately 20% in the USA [22].

Patient selection may have some bearing on this – in Sheffield we rarely have patients referred with other than newly diagnosed disease; we do not have patients who have proved difficult management problems to other clinicians (e.g. chemotherapy resistance). In addition, whilst we stress that there is no clinical indication for routine use of second uterine evacuation, in selected cases with persisting mild symptoms and lower levels of hCG we may recommend this, thus reducing the number of patients requiring chemotherapy [16]. However, we do not have an 'inferior' cure rate – 98% overall – from this ultra-conservative policy.

The risks of treating a greater proportion of patients are theoretically the same as those quoted for prophylactic chemotherapy – mainly exposure of twice as many patients to toxic therapy. In practice, however, chemotherapy though associated with short-term side effects has not led to major long-term sequelae – in particular on future pregnancy outcomes, and only a moderate increase in second cancers [23].

The regimen of chemotherapy given varies in type, schedule and with clinical treatment criteria. Here, staging/prognostic groupings become highly relevant – there is clearly a need to distinguish low-risk from high-risk molar disease and particularly which factors relate to GTN and to chemotherapy resistance. There are a large number of classification schemes for both scoring and staging GTN, none of which has gained universal acceptance, reflecting both 'personal preference' on the part of the proponents and users of the particular system and also that there are deficiencies in all of them [24]. The World Health Organisation (WHO) (and the Charing Cross system from which it is derived) and the National Institutes of Health (NIH) systems are the oldest and still widely used. They are not true staging systems but define (with reasonable accuracy and equivalence) prognostic categories requiring 'high-risk' (multi-agent) and 'low-risk' (single-agent) chemotherapy. The revised International Federation of Gynecology and Obstetrics (FIGO) system now includes prognostic as well as anatomical criteria [5] and has been retrospectively tested [25]; in a prospective evaluation the system proved reliable except that over 60% of patients who scored 6 (classified as low risk) required alternative chemotherapy [26].

The Charing Cross group, using their own scoring system, previously selected three groups for differing intensities of therapies; most centers, however, define two groups only, and this is also now the practice at Charing Cross. Single-agent intramuscular methotrexate, with folinic acid rescue,(IM MTX/FA) remains the most popular therapy worldwide for truly low-risk GTN [27]. Treatment is continued for 6 weeks after the hCG level has normalized {28] However, dactinomycin given as a single agent treatment has also been shown to be effective [29}; indeed results from a randomized Gynecology Oncology Group study show that pulse dactinomycin is better than pulse methotrexate [30]. However this way of giving methotrexate is not typical of world-wide (other than US) practice. Methotrexate has its own particular problems [31] and even ardent proponents of this therapy admit that toxicity curtails the use in over 5% of patients (the associated pleurisy can be particularly debilitating). Dactinomycin causes alopecia,

myelosuppression, nausea and vomiting. Despite the fact that this might seem to be a more cost-effective way of managing treatment (i.e. two-weekly intravenous day case injections rather than alternate-day intramuscular injections) patients often prefer the latter particularly if this can be done in the community. Also there are more data on methotrexate, than on dactinomycin, as to the lack of long-term carcinogenicity.

In the UK we have recently evaluated the complete response rates in patients with low risk GTN treated with single agent IM MTX/FA. Significantly higher rates of resistance were found for patients with FIGO/WHO risk score of 6 or hCG level of >100,000 iu/l. though all patients were eventually cured with chemotherapy or surgical salvage. We suggested that revision of the FIGO/WHO scoring system may be appropriate to enable selection of more effective first line chemotherapy [32]. We have also confirmed that complete response after first-line management was not significantly different between Stages I and III disease [33]

A proportion of patients will be resistant to single-agent chemotherapy but almost always respond to multi-agent regimens.

For high-risk tumors multi-agent chemotherapy (MAC, EMACO, MEA [34,]) are given with good result; and, even when these patients are chemoresistant, salvage regimens incorporating agents such as cisplatin (EMA/EP or TE/TP) are successful in the majority of patients [35]. In ultra-high risk GTN more intensive chemotherapy, with regimens such as these, should be considered from the start. In a recent UK study 196 high-risk patients were treated with EMA/CO or MEA. The overall survival was 94%, with a median follow-up of 4.69 years.[36

The treatment of CNS disease differs between centers. Charing Cross gives CNS prophylaxis for very high risk disease; in Sheffield we have not found this necessary [37]. For established CNS disease in the USA radiotherapy is often given early [38]. In the UK stereotactic radio-surgery is used with small lesions. Otherwise resective surgery, where possible, precedes chemotherapy with a regimen containing intermediate dose systemic, and intrathecal, methotrexate [39].

Choriocarcinoma following live birth was reported to be associated with poor prognosis [40]; but this may have reflected other associated features (late diagnosis, high hCG levels, multi metastatic disease) rather than the diagnosis per se.[41] Nowadays, in this group, and in non-term choriocarcinoma, multi agent chemotherapy is generally recommended and is usually curative. However , in a recent UK study of 65 patients with low risk gestational choriocarcinoma not all required chemotherapy and in those that did single agent IM MTX /FA was successful in 43% and all patients were subsequently cured [42].
Death from GTN is fortunately extremely rare when patients are treated at expert centres [43]

22.6 FOLLOW-UP

Patterns of clinical and hCG surveillance for further molar problems

vary across the world, determined by local factors and also by knowledge of the difference in risk of sequelae between complete and partial moles. For example the likelihood of GTN (requiring chemotherapy) after partial mole is less than 2.0% [44]; however malignant change can occur [45] and limited surveillance is still essential in this group of patients. With complete mole the risk of GTN is greatest in the first few months following diagnosis and it is a sensible convention to ask patients to avoid further pregnancy for 6 months of normal hCG levels to enable efficient hCG follow-up. In fact if the hCG is normal at the time that this is first measured following evacuation there is virtually no risk of the patient developing GTN [46].

In the past advice on contraception varied across the Atlantic – in the UK we recommended avoiding oral contraception until the hCG level had returned to normal. North American clinicians consider the risks of further pregnancy greater than the risks of using the pill and are happy to prescribe this immediately following molar evacuation. Nowadays, in the UK, as in mainland Europe, we recommend that oral contraception can be safely given after evacuation[3] However, should pregnancy occur in this period a normal baby usually results.

It is now clear that "unexplained" persistent low level hCG elevation may be seen in three clinical scenarios – where there is:

- a past history of gestational trophoblastic disease ("quiescent GTN")
- no history of GTD ("unexplained elevated hCG")
- false positive hCG elevation ("phantom hCG")

Patients reported from all groups have often been treated unnecessarily with chemotherapy and/or hysterectomy, classically without hCG response, so it is important that clinicians are aware of these syndromes, reinforcing the need for the involvement of expert specialist teams. Indeed in a recent UK series [47] 14 women presented with persistently elevated hCG of unascertained origin. In 10 cases no evidence of GTN has so far been found. Many go on to have healthy pregnancies but there is still the possibility that GTN in some form will eventually become manifest Long-term follow-up of such cases is therefore mandatory.

22.7 SPECIAL SITUATIONS

Undoubtedly, whilst conventional chemotherapy is successful in almost all cases [48] certain situations mandate a more intensive approach – this scenario has been termed ultra-high risk GTN. However, where there is a large tumor burden (for example, in the lungs) it is prudent to consider lower starting doses of induction chemotherapy to avoid hemorrhagic and tumor lysis complications

With ectopic moles the clinical presentation is similar to any other ectopic pregnancy. Histopathologically these are over-diagnosed [49] and the outcome is similar to other cases of GTN [50,52].

The scenario of twin mole and viable foetus is often misdiagnosed clinically but, once confirmed, about 1 in 3 pregnancies will result in a normal baby. Pregnancy complications are however frequent. GTN is not uncommon but when treatment is required it is invariably successful [52].

Placental site and epithelioid trophoblastic tumours are rare but distinct categories of GTN. The FIGO scoring system cannot be applied - for example, hCG production is not an accurate reflection of tumour burden. Truly localised disease can be cured with hysterectomy alone. Metastatic disease is less chemo-sensitive than in other GTNs [53]

22.8 CONCLUSIONS

For the optimal management of GTD (allowing for geographical and cultural variations) it is possible to recommend the following:

- Patients diagnosed with GTD should be formally registered and monitored through a purpose-designated screening center.
- Clinical management should be by a multidisciplinary team of expert specialist health professionals.
- All staging/scoring systems have deficiencies but are appropriate guides to clinical management when used by clinicians familiar and expert in interpretation of the particular system. However, a unified approach has been adopted in the FIGO 2000 staging and scoring system which is now gaining world wide acceptance (see chapter 6)
- An assay that detects all or as many forms as possible of βhCG is essential (see chapter 4)
- Standard (i.e. non-research) investigations should be appropriate to that information required for the staging/scoring system being used.
- Prophylactic chemotherapy is only acceptable for those patients with high-risk molar disease where monitoring facilities are suboptimal (see chapter 15).
- Hysterectomy is an option for older patients with molar disease not requiring to maintain fertility.
- Low- and high-risk categories of GTN can be defined, though some overlap is inevitable.
- For low-risk disease single-agent chemotherapy with methotrexate or dactinomycin is appropriate; methotrexate is generally considered the less toxic in the short and long term (see chapter 16).
- For high-risk disease multi-agent chemotherapy (usually incorporating methotrexate, dactinomycin and etoposide, most popularly EMA-CO) is recommended (see chapter 17)
- Relapse after first-line chemotherapy for high-risk disease can

often be salvaged by alternative platinum-containing chemotherapy regimens (EMA/EP, TE/TP) plus surgical resection when appropriate.

- Ultra-high risk GTN (and PSTT/ETT) warrant different management strategies (see chapters 18,20)
- In the optimal situation almost 100% success can be achieved in the treatment of GTN.
- Follow-up is usually dictated by local circumstances, but due regard must be paid to long-term effects of therapy (see chapter 23) though most patients lead normal and fertile lives.

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