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Ultra high risk GTN: what is it and how should we manage it?

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18.1 INTRODUCTION

The term “ultra high risk” GTN probably means slightly different things to different investigators. However, it is perhaps best considered as any presentation of GTN that might be associated with either early death within weeks of starting chemotherapy or poor long-term survival. The term should probably only be applied to choriocarcinoma (CC) and not placental site or epithelioid trophoblastic tumours (PSTT/ETT) which are different disease entities, and often associated with a poorer long-term prognosis. Unlike CC, PSTT/ETT demonstrate a different biological and clinical behaviour and the scoring system used to determine risk of resistance to single agent chemotherapy is not helpful in their management. The management of PSTT and ETT is discussed further in chapter X.

Several factors have been implicated in increasing the risk of early death from GTN including very advanced disease resulting in fatal haemorrhage and/or organ failure. Likewise a number of factors have been associated with reduced long-term survival often as a consequence of the development of drug resistance. Unsurprisingly, those patients with very advanced disease will require considerably more chemotherapy and so a proportion of those might be expected to develop resistance along the way. However, it turns out that the interval of time from the last known or causative pregnancy is also important as well as the sites of disease involvement. In what follows, we will discuss the clinical variables associated with ultra high-risk disease and the management strategies that can be employed to help improve outcomes.

18.2 FACTORS ASSOCIATED WITH EARLY DEATH, AND MANAGEMENT ADVICE

Any death from GTN is a tragedy, but early deaths occurring before the

disease has had a chance to respond adequately, due to either complications of the disease or treatment, are particularly distressing. With prompt specialist intervention and high quality intensive support, many of the potential causes of early death can be averted. In a recent review of 196 patients with high risk disease treated at the two treatment centres in the UK between 1995 and 2010, just two patients (1%) died within 4 weeks of presentation, one from cerebral haemorrhage and the other from massive pulmonary embolism (Agarwal et al, 2014).

Patterns of disease that give cause for concern and that may be a feature of ultra high-risk disease and/or are associated with potentially fatal haemorrhage include:

- Pathological or suspected diagnosis of choriocarcinoma (CC)
- Multiple (>20) pulmonary metastases or associated with haemoptysis
- Brain metastases
- Large volume liver metastases
- Profuse vaginal bleeding
- HCG > 1,000,000 I.U./L
- Interval since last antecedent pregnancy of >2.8 years

Patients with CC require urgent evaluation and treatment. The disease can progress rapidly with a tumour doubling time which can be of just a few days or less. Rapid haematogenous spread of metastases to the lungs and also, sometimes to liver, brain, kidneys, bone and indeed any site can occur. The presence of liver, with or without brain metastasis, is always indicative of ultra-high-risk disease. Disease like this and/or widespread metastasis is associated with both a higher probability of drug resistance and of life-threatening complications, notably intra-tumoural haemorrhage due to the profuse and fragile vascularity of the metastases, especially during the initial phase of treatment as initial tumour shrinkage takes place.

Lung metastases are common in GTN and the number of lesions contributes to the FIGO prognostic score with >8 metastases on chest radiograph contributing 4 to the overall score. Some patients, especially those with CC, may have dozens or even hundreds of lung metastases and these may cause

respiratory distress especially if there is delay in instituting effective treatment. Additionally, because the metastases are highly vascular, they may bleed either spontaneously or in response to chemotherapy as the cellular disruption associated with tumour necrosis take place.

Patients with large numbers of lung metastases and/or haemoptysis need very careful monitoring of oxygen saturation and respiratory rate with a low threshold for referral to a high dependency or intensive care unit for respiratory support. Ideally, patients should be managed with high flow oxygen and continuous positive airways pressure (CPAP) external respiratory support but, occasionally, intubation and full ventilatory support will be required. The need for ventilation is a grave sign as the positive pressures involved in ventilation increase the risk of fatal haemorrhage into the lungs from the friable rich tumour vasculature. Early extubation and nursing of patients with the head down to enable drainage of blood out of the lungs has, in our experience, been lifesaving while response to chemotherapy takes place. It is at present not clear whether extracorporeal oxygenation may also help in patients who cannot be safely extubated. .

Brain metastases are rare in GTN. Estimates for the approximate risks of developing GTN with CNS disease are 1 in 400,000 for all pregnancies, 1 in 22,000 for all molar pregnancies, 1 in 1600 for patients with post-molar pregnancy GTN and 1 in 6 for patients with non-molar choriocarcinoma (Savage et al 2015).

Brain metastases are chemosensitive and usually curable with chemotherapy. Survival rates are likely to be as high as patients without brain metastasis provided the initial period of treatment is managed optimally (Newlands et al 2002). Haemorrhage into a brain metastasis may occur and require neurosurgical intervention to relieve raised intracranial pressure and control the haemorrhage. In one series, 5/27 patients with brain metastases required surgery to deal with life threatening complications, even though low dose induction chemotherapy was used in the majority (Savage et al 2015). Sometimes, simply raising a skull flap to enable the brain to expand upwards rather than downwards through the foramen magnum is all that is required to relieve the raised intracranial pressure that can occur when commencing chemotherapy in advanced brain disease.

External beam whole brain radiotherapy is not recommended as part of curative therapy as there is no evidence that this improves outcomes. Moreover, there are ample data from other tumour types showing how it can enhance toxicity with impaired memory and increased risk of second malignancies in later years. The radiotherapy will also increase the risk of toxicity from intrathecal methotrexate. However, targeted radiosurgery (gamma knife) or stereotactic external beam radiotherapy to the lesion(s) may reduce the risk of complications and help sterilize residual abnormalities after chemotherapy. As experience is likely to remain limited due to the rarity of the condition, definitive treatment recommendations cannot be made; each case needs to be considered on its merits and a multidisciplinary plan between oncology and neurosurgery formulated with regular review of clinical progress along with hCG levels and follow-up imaging. The establishment of an ultra-high risk disease database within the ISSTD should help refine management over time.

Liver metastases are usually a feature of large volume disease and very high hCG levels. Intra-tumoural haemorrhage can occur and may on occasions require interventional radiology or surgical intervention. Liver metastases generally respond to chemotherapy but are associated with a higher rate of drug resistance, especially if the interval since last antecedent pregnancy is long (Ahamed et al 2012). The role of local intervention for residual disease in the liver such as resection of metastases or radiofrequency ablation is not defined but may be considered in selected cases.

Profuse vaginal bleeding, unlike the other features of ultra high-risk disease, may also be a feature of persistent molar disease. Sadly it remains an occasional cause of death in GTN that should be preventable with high quality and rapid intervention. Heavy vaginal bleeding is an indication for chemotherapy in GTN and usually settles over a few days as the treatment takes effect. However, on occasions life-threatening haemorrhage will occur despite transfusion before or during the first few days of chemotherapy. Where possible, embolization of the feeding uterine arteries is the preferred treatment modality as this is usually effective and enables the woman to retain her uterus and subsequent fertility (McGrath et al 2012). However, emergency packing of the uterus or vaginal metastasis or alternatively

hysterectomy remains necessary in occasional patients and it is vital that, whenever possible, patients with profuse vaginal bleeding are known to and assessed by the gynaecological surgeons before crisis intervention is needed. Such patients are probably best managed on a gynaecology ward with theatre facilities nearby so that an emergency hysterectomy can be actioned within minutes when there is no less invasive alternative.

HCG levels are a good surrogate for tumour bulk and in ultra-high risk patients hCG levels in excess of 1,000,000 I.U./L may occur. Patients with very high volume chemo-sensitive disease are also at risk of tumour lysis syndrome. The risks of this can be reduced by vigorous intravenous hydration, allopurinol or rasburicase and careful attention to electrolyte balance (notably potassium levels) and renal function.

Other potential causes of death include neutropenic sepsis from chemotherapy, although with use of haematopoietic growth factors and appropriate antibiotics this should no longer happen. Thrombo- or tumour-embolism is a potential cause of death, especially in ill bed-bound patients. Additionally, active bleeding or concerns about the risks of treatment-induced haemorrhage may prevent the use of prophylactic anticoagulation. In the absence of active bleeding the benefits of low molecular weight heparin thromboprophylaxis probably outweigh the risks. Alternatively, a continuous heparin infusion can be used which is faster to reverse if bleeding arises. However, anticoagulation may be contraindicated and if there is radiological evidence of proximal leg vein thrombosis, the placement of an inferior vena cava filter may be indicated.

Retrospective review of large case series has suggested that the interval since last antecedent pregnancy is a prognostic factor for the development of drug resistance (Powles et al 2006). In this report, multivariate analysis was used to investigate if the time interval was of prognostic significance in a cohort of 241 high-risk patients with GTN. Subsequent cut-point analysis was used to determine an optimal cut-point for the interval covariate. A period of greater than 2.8 years after pregnancy was found to be of most significance. The 5-year overall survival was 62.0% (95% CI: 47–76%) for greater than 2.8 years versus 94% (95% CI: 91–97%) for less than 2.8 years (P=0.001).

Interestingly, significantly fewer early deaths have occurred since the mid 1990s in the supra-regional service provided in the UK to all patients with GTN (Alifrangis et al 2013). For example at the Charing Cross Trophoblastic centre, although the frequency of liver and brain metastases has not changed over the past two decades, the early death rate fell from 7.8% (11/140) to 0.7% (1/140) (P=0.0058). This coincides not only with improved oncological and intensive care support over the past 20 years but also the introduction of low dose induction chemotherapy with weekly cisplatin and etoposide for 1-3 weeks (described below) before starting standard chemotherapy.

The rationale for this approach has been that a more gradual reduction in tumor volume reduces the risk of significant hemorrhage in critical organs in patients with high-volume disease. Patient selection for induction chemotherapy is dependent on clinical judgment of disease volume, particularly within the thorax, the presence of brain and/or liver metastases, and an overall assessment of the risk of organ failure and early death. In our experience, patients who require EP induction chemotherapy have a higher number of metastases (\geq six metastases), higher hCG (average \geq 700,000 IU/L), and/or higher total FIGO score (\geq 12) (Alifrangis et al 2013).

18.3 FACTORS ASSOCIATED WITH LATE DEATHS, WITH MANAGEMENT OPTIONS

Ultra-high risk GTN is associated with a higher frequency of resistance to standard first-line chemotherapy with methotrexate and etoposide based regimens. This is especially the case in patients with extensive liver metastases, multiple brain metastases and those with a prolonged time from the antecedent pregnancy.

Careful and regular monitoring of hCG levels to detect drug resistance and an early switch to cisplatin based chemotherapy with EP-EMA or TP/TE will prevent most patients from developing drug resistance. In selected cases there may be a role for salvage surgery, especially hysterectomy. Additionally, occasional salvage is possible with high

dose chemotherapy and haematopoietic stem cell support (El Helw L et al 2005) although the indications for this procedure are poorly defined in GTN.

On a cautionary note, in our experience, some patients failing salvage chemotherapy have proved, on later histology, to have placental site, epithelioid trophoblastic or mixed tumours.

18.4 INVESTIGATION

Patients with ultra-high risk GTN must start treatment as soon as possible and investigations should not delay this. Essential investigations are hCG measurement, full blood count, coagulation screen, renal and liver function, urate, cross sectional imaging of the pelvis with Doppler ultrasound and if available a MRI, a contrast enhanced CT chest and abdomen and if not immediately available a chest radiograph and ultrasound abdomen plus a brain MRI or, if not readily available, CT brain scan. All CT and MRI imaging should be contrast enhanced. Microbubble ultrasound can help in distinguishing liver metastases from benign lesions if there is doubt. A FDG-PET CT is unlikely to alter initial management and so is not part of routine initial assessment. Lumbar puncture should be performed once head imaging has been done to determine if this procedure is safe. This will enable assessment of hCG levels in the CSF as well as cytology, protein and glucose to search for very rare meningeal involvement. A hCG CSF:serum ratio of > than 1 : 60 is suggestive of CNS involvement.

Treatment for ultra high risk GTN should be started on the same day of admission, and not delayed for a lumbar puncture, given the rapid growth rate of this cancer; a delay of just 1-2 days may transform curable into incurable disease. Blood should be cross-matched in case of haemorrhage. Regular observations of pulse, blood pressure, oxygen

saturation, temperature and fluid balance should be performed throughout the early phase of treatment. Appropriate support services should be notified of the potential need of their engagement at short notice. For example, if there are brain metastases, then the neurosurgeons should be made aware of the patient. Similarly, if there are haemorrhagic liver metastases then the interventional radiologists and liver surgeons should be alerted. In all cases of ultra high-risk disease, the intensive care and or high dependency units should be briefed and if the risks are judged to be very high, the patients should be initially managed in this environment even if they appear well.

In patients who have relapsed or developed resistant disease, all the above tests need repeating including a whole body FDG-PET CT scan. The latter can help to reveal which disease sites are active and might be suitable for potential curative surgical resection (Dhillon et al 2006).

18.5 TREATMENT

Several multi agent chemotherapy regimens have been used for ultra-high risk GTN (table X.1). Probably the greatest experience is with EMA/CO developed by the Charing Cross team and now the standard regimen for all high-risk patients in the UK. However, to minimise the risk of catastrophic haemorrhage during the first few weeks of therapy in patients with extensive lung metastases and/or liver or brain involvement, we have employed a relatively gentle weekly induction regimen of cisplatin 20mg/m² and etoposide 100mg/m² (low dose induction EP) on days 1 and 2 repeated weekly for one to 3 weeks. This, combined with high dependency support, has been successfully used and is associated with an almost complete elimination of early deaths, resulting in improved overall disease outcomes in recent years.

In those patients with ultra-high risk disease with poor long-term prognostic factors such as combined liver and brain metastases we are now favouring the use of EP/EMA once the acute period on low dose

induction EP has passed. Those patients with brain metastases should have the methotrexate (MTX) dose increased to $1\text{g}/\text{m}^2$ with additional folinic acid rescue and intrathecal MTX 12.5 mg given with the CO or EP provided it is safe to do a lumbar puncture (Newlands et al 2002). In those patients where there is a risk of third space pooling of MTX then employing TP/TE may be valuable beyond the induction low dose EP. Whilst M-EA has been a very successful regimen, it is a little less practical to give in terms of frequency of visits and overnight stays and so has now been replaced with EMA/CO and EP/EMA. The latter is very toxic and great attention to renal and bone marrow function is required. If intensity cannot be maintained with EP/EMA using G-CSF support then a switch to the two weekly alternating TP and TE can be very helpful (Wang et al 2008).

18.6 PROGNOSIS AND FUTURE DIRECTIONS

Survival prospects for ultra-high risk GTN with optimum intensive support and appropriate chemotherapy are around 70-90% depending on sites of disease and duration of last known pregnancy. Early deaths are generally avoidable and although resistance to first line chemotherapy is quite common, salvage with cisplatin-based regimens with or without hysterectomy or resection of other disease sites and, in selected cases, high dose chemotherapy with haematopoietic stem cell support will salvage the majority of patients.

Future research is required to compare the available salvage regimens (EP-EMA and TP/TE) and identify new agents for the occasional patient with cisplatin refractory disease.

18.7 SUMMARY AND CONCLUSIONS

Ultra-high risk GTN is rare and presents management challenges. Intensive specialist support is required to help patients through the critical early phase of treatment. Induction chemotherapy with low dose weekly etoposide and cisplatin may be indicated prior to initiating standard combination treatment. The prognosis is good

although one third of patients will develop drug resistance to etoposide and methotrexate based regimens and require salvage with cisplatin based treatment. The establishment of an ISSTD ultra high-risk patient database will hopefully help to provide more information on prognostic factors to enable improved management of these rare patients.

Table 18.1 Metastatic chemotherapy regimens

Chemotherapy regimens used successfully in PSTT

EP-EMA	etoposide/ cisplatin alternating weekly with etoposide, methotrexate and dactinomycin (Actinomycin D)
EMA-CO	etoposide, methotrexate, dactinomycin alternating weekly with cyclophosphamide and vincristine (Oncovin)
M-EA	methotrexate alternating with etoposide and dactinomycin
TP/TE	paclitaxel and cisplatin alternating two weekly with paclitaxel and etoposide

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