25
FUTURE PROSPECTS
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25.1   REFERRAL CENTERS FOR PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE

A major part of the success in the management of gestational trophoblastic disease (GTD) and gestational trophoblastic neoplasia (GTN) has been the development of regional or national centers for these patients' management. By focusing on the variations in clinical presentation, treatment, management and complications, the outlook for these patients has improved progressively over the past four decades. The success for any center managing GTD and GTN needs the following elements:

1. registration of patients with or at risk of GTD or GTN, comprising clinical background details and arranging for regular human chorionic gonadotropin (hCG) estimations on each patient;
2. a sensitive and reliable assay for hCG. This will be considered further below;
3. nursing and medical staff experienced in the diagnosis and management of patients with this disease who can deal with the numerous queries both from their referring gynecologists and from the patients and their families;
4. the national or regional centers need to be in a position of good transport to enable patients to come for treatment and consultations;
5. a reliable postal service for sending the patients' samples to the center and for posting back the hCG results;
6. good patient compliance with sending hCG samples and attending for treatment.

The above requirements are met in those parts of the world where regional or national trophoblastic disease centers have developed. There are many countries where it would be possible to develop new regional or national centers along the lines of those already existing and where the basic requirements of a regional center could be put in place if there was appropriate co-operation between the gynecological community of that country and the health care commissioners and providers. In countries where the above key elements for developing a regional center are lacking at present, clinicians dealing with this disease need to develop links with one of the existing regional centers in another country to discuss management policies and difficult cases. Dissemination of this expertise is one of the key purposes of this

volume by describing the policies of some of the existing regional and national centers.

25.2   QUALITY CONTROL OF hCG ASSAYS

The key role of assays for hCG has been emphasized throughout this volume in the diagnosis, monitoring and clinical management of these patients. In Chapter 5(?#), the key aspects of different hCG assays have been reviewed.

The range of biological functions of hCG which is produced throughout pregnancy remains unclear. It is feasible that hCG could perform both a growth-promoting and growth-modulating role in a normal pregnancy. hCG and its fragments may also have a growth-promoting role for the abnormal trophoblastic cell in GTD and GTN. This could explain the clinically observed phenomenon that the abnormal trophoblast in GTD and GTN rarely grows clinically without producing detectable hCG.

Modern automated hCG immunoassays may be extremely efficient, fast and very effective in detecting normal pregnancy. The combination of antibodies used in these tests, and the polyclonal antiserum used in older radioimmunoassay tests may not necessarily be optimal, however, for monitoring GTD and GTN. This is because hCG exists in a number of hCGβ immunoreactive forms. Regular hCG, hyperglycosylated hCG (hCG-H), nicked hCG, nicked hCG missing the β-subunit C-terminal peptide, regular free β-subunit, nicked free β-subunit and hyperglycosylated free β-subunit are present in serum in GTD and GTN cases. The same molecules and β-subunit core fragments are present in urine samples. Any one of these many hCG-related molecules may be the principal source of immunoreactivity in patients with GTD or GTN, prior to or following therapy, or during a recurrence.

As emphasized in Chapter 5 (? #), assays can underestimate or miss GTD and GTN. At present the recommendation for an hCG assay for screening, monitoring and following up patients with GTD and GTN is that the assay should detect all the main forms of hCG and its free β-subunit and fragments. In the future it may be possible to subclassify different variants of GTD and GTN by the profile of the proportion of hCG and its metabolic degradation products that are produced.

Indeed, previous work has suggested that free β-hCG is the predominant form of the hormone produced by patients with PSTT, whilst an elevated hCG-H appears to be a marker of invasive disease (1, 2). However, emerging data suggests that a high free β-hCG is also seen in some patients with choriocarcinoma and non gestational tumors so this does not appear to be specific for PSTT(3). Further work is now necessary to confirm these findings.

A better understanding of the profile of hCG and its degradation products produced by different forms of GTD and GTN would help clarify some of the problems of monitoring patients whose serum or

urine samples contain immunologically reactive substances that are detected on assays directed against the β-subunit of hCG. Many serum assays for hCG have allotted an upper limit of normal of between 2-5 IU/l. It is not all that rare for some patients to have values in the range of 5—50 IU/l. With long-term follow-up, confidence increases in that whatever has been detected in the hCG assay does not appear to have biological significance or association with any other recognized disease.

The syndrome of unascertained persistent low level hCG elevation is now well recognized (4)); in such cases it is important to exclude false positive results and also to bear in mind that low level hCG production (of pituitary origin) can be normal in menopausal women (5).

In diagnosis and monitoring of GTD and GTN, it is important that an assay has a minimal potential to yield false positive results. It is also now recognized that hCG assays can have false negative results (6) but the full implications of this on clinical outcomes require further investigation. The emerging role of hyperglycosylated hCG in this and other clinical situations is discussed in Chapter 5 (?#).

ASSESSING DISEASE STATUS

Whilst sophisticated imaging technologies have given us more knowledge of the behavior of GTD they have not generally helped in routine preliminary assessments, though they may be helpful in defining the localization and extent of primary disease and particularly recurrence. One exception may be measurement of the Uterine Artery Pulsatility Index (UAPI) - a recently published study (7) has revalidated the usefulness of UAPI as a predictor of methotrexate resistance (MTX-R) independent of FIGO score. Though MRI does not have a role in routine assessment of pelvic disease, it is sometimes used as a problem-solving tool to assess the depth of myometrial invasion and extrauterine disease spread in equivocal and complicated cases, suspected PSTT, and recurrent GTN. PET/CT is fast emerging as a promising tool for disease mapping, monitoring treatment response, and identifying recurrent or residual disease after chemotherapy (8). Prudent use and evaluation of these imaging techniques may permit early diagnosis and appropriate management, contributing to excellent cure rates of the disease

The ultimate aim of risk scoring patients is to select those most likely to respond to single agent chemotherapy. Recent studies have suggested that the present cut-off between FIGO 2000 low and high risk disease is too high – patients with risk score 6 and/or very high hCG levels are particularly likely to require second line chemotherapy (9).

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25.3 MOLECULAR GENETICS

Our knowledge of the molecular genetics of GTD and GTN has developed rapidly over the last two decades. However, at present we do not know whether there is a common genetic event which is the final cause of all the variants of GTD and GTN. In the future it will be important to identify what this mechanism or mechanisms are, to understand the disease process better and the process which makes gestational tumors so much more chemosensitive than the majority of the more common human cancers. At present we do not comprehend the maternal defect in the ovum which allows the abnormal fertilization to occur in complete and partial moles.

However, recent work in families with inherited repetitive biparental hydatidiform moles, which phenotypically appear as complete moles (CHM), has identified mutations in NALP7 (NLRP7) as the likely cause in perhaps 75% of cases (10); Fallahian, 2013 #524}. Another 5-10% of cases may be explained by mutations in another gene called KHDC3L but additional causative gene(s) that possibly lie in the same phenotypic pathway remain to be discovered (11). Affected individuals appear to nearly always have molar pregnancies. The function of the normal genes and the affect of the mutations is still unclear but could regulate imprinting (12) As the abnormal gene maybe expressed throughout the genital tract it is also unclear whether the resulting molar pregnancies occur because of defects in the egg or the environment in which the fertilized egg develops. However, since egg donation from an unaffected individual has enabled normal pregnancies to occur, it seems likely that the defect resides in the egg and affected women can now have children (13)

Clearly, given the rapid developments in molecular genetics (Chapter 2), it is likely that we will continue to be able to subtype variants of GTD and GTN which will help clinical and management decisions. This is illustrated by the clinical heterogeneity of placental site trophoblastic tumors (PSTT) and the fact that these tumors can occur after both a normal biparental pregnancy, an androgenetic complete molar pregnancy and a partial hydatidiform mole.

Provided DNA is available from the tumor, patient and partner, the presence of paternal genes can now be usually confirmed, even from formalin-fixed blocks. The presence of paternal genes in the tumor is definitive proof of gestational origin (14). However, inability to detect paternal genes in a trophoblastic tumor cannot exclude gestational origin but can make it unlikely. Using multiple microsatellite polymorphisms, which fail to detect any paternal genes in the tumor, combined with an atypical clinical picture, can make it reasonably certain that the patient does not have a gestational tumor. Morphologically it is not always possible to distinguish gestational choriocarcinoma from tumors with extensive trophoblastic differentiation. This additional genetic information can alter clinical decision-making. If it seems very unlikely that the patient has a gestational tumor, then the management should be directed towards disease control and palliation since nearly all these patients will

succumb from their disease. In contrast, patients with paternal genes in their tumor continue to have the good prognosis associated with gestational choriocarcinoma and most of these patients can be salvaged with appropriate treatment. The one exception might be patients with PSTT/ETT where the interval from the causative pregnancy is more than 4 years. Where there have been multiple gestations, genetics can help determine which gestation was causative of the PSTT/ETT. In the future, in the absence of tumour biopsy material, it may be possible to make this type of genetic diagnosis from a blood test by extracting circulating tumour DNA, the so called liquid biopsy.

25.4 MOLECULAR BIOLOGY

With the identification of NLRP7 and KHD3CL as key genes involved in the development of recurrent bi-parental CHM there is now an urgent need to understand how the corresponding proteins work. Unfortunately knock-out studies in mice are not possible as these animals lack equivalent genes which might explain why this disease is not seen in these animals. Consequently, alternative strategies are required including RNAi-mediated knockdown or CRISPR silencing in model cell systems and molecular modeling/bio-informatic based studies. Once we understand how these genes function in health and disease we may be able to extrapolate the findings to other GTD settings where mutations in NLRP7 and KHD3CL have so far not been seen. Indeed, it is very likely that there are other genes involved which may or may not be linked to NLRP7 or KHD3CL function. While the precise molecular pathogenesis of hydatidiform mole and choriocarcinoma has not been determined, various oncogenes and growth factors have been studied in these tissues. For example, enhanced expression of several members of the epidermal growth factor receptor family is seen particularly in GTD with increased malignant potential (15). Increased expression of p53 gene and c-fms has been reported in complete molar pregnancy (16, 17). Rearrangement of c-fms and amplification of c-myc has been shown in a study of five choriocarcinoma cell lines and increased c-myc and ras RNAs have been measured in choriocarcinoma (18, 19). However, it is important to emphasize that normal placentae have also been demonstrated to express high levels of several proto-oncogenes. Additional studies need to be pursued to further understand the potential relationship between alterations in the expression of various oncogenes and growth factors and the pathogenesis of GTD. Differential expression of oncogenes may also be of prognostic importance in identifying trophoblastic tumors with marked virulence.

Certain genes are only expressed on the maternal or paternal chromosomes (parental imprinting). Tumor formation has been associated with modification of parental imprinting and complete hydatidiform moles appear to have relaxation in parental imprinting. Relaxation of parental imprinting may be important in the

pathogenesis of trophoblastic neoplasia.

25.5 OMIC TECHNOLOGIES IN GTD RESEARCH

The advent of high through-put screens using geneomic, proteomic, metabolomic and other omic technologies promises to revolutionise many areas of medical practice. Thus far, however, comparatively little has been done in GTD. This has partly been because of the lack of fresh tissue. Fortunately, new techniques are evolving that enable the use of formalin fixed and paraffin embedded material for these omic approaches. Thus, the 'fresh tissue obstacle' should no longer be a substantial barrier to this type of research. So what could this do for GTD in the clinic? The identification and development of new molecular signatures that predict which CHM/PHM is destined to become malignant at or soon after evacuation would be useful. This would avoid the many weeks and sometimes months of uncertainty for women undergoing hCG surveillance following molar evacuation. If such a test were made, women identified as having malignant moles could be assigned to chemotherapy immediately and those with benign disease could be reassured and allowed to get on with normal life. It is also conceivable that a molecular signature of resistance to single drug therapy might be discovered which would help refine the FIGO scoring system. Over the next 10 years we should hopefully see several exciting developments in this area.

25.6   INTENSIVE CARE FOR PATIENTS PRESENTING WITH ADVANCED DISEASE

Patients with organ failure from GTD or GTN present a range of major medical problems. Some of these have been discussed in Chapter 8. These patients constitute one of the two subgroups of patients with GTN who die from their disease. Here the usual cause of death is organ failure from extensive disease before adequate chemotherapy can be given. The most common problem which needs intensive care support in these patients is respiratory failure from multiple pulmonary metastases. If the patient is breathless at rest before chemotherapy is started, it is likely that their respiratory function will deteriorate further when they start chemotherapy. This syndrome of presumed tumor lysis, inducing reduced pulmonary compliance and oxygen exchange, can present a major clinical dilemma. Administering induction chemotherapy with low doses of etoposide and cisplatin reduces the risk of respiratory failure resulting in higher cure rates (20). It is important not to ventilate the patient with high ventilation pressures which will disrupt the remaining compliant lung. At least in some patients this complication can be reduced by starting dexamethasone at the time the patient starts chemotherapy. Patients who arrive intubated should be extubated at the earliest possible opportunity. The possibility of extra-corporeal

oxygenation has also been mooted on many occasions but to do this requires full anti-coagulation which in itself may be risky as these tumours are highly vascular.

Patients with single cerebral deposits from GTN which are superficial should usually have these removed or irradiated at the initiation of therapy to minimize the chance of intracerebral hemorrhage. However, if there are multiple cerebral metastases, this is not possible and it is important to prevent cerebral edema developing at the initiation of therapy. The third major organ that can fail at the initiation of therapy in a patient with GTN is the liver. Extensive intrahepatic metastases which can hemorrhage can result in hepatic failure and major clotting problems. Again, the use of low dose induction etoposide and cisplatin has helped to avoid early deaths in this situation often from haemorrhage and or organ failure. Provided the patient can be supported through the acute phase, recovery of liver function will occur as the tumor comes under control. The use of embolisation through interventional radiology may also be helpful. However, it should be recognized that the presence of liver metastases in a patient with GTN continues to be a significant adverse prognostic factor although survival has improved in recent years (21).

25.7 HIGH-DOSE CHEMOTHERAPY

The techniques for safely performing high-dose chemotherapy with autologous stem cell rescue improved rapidly over the last two decades of the 20th century. Advances included peripheral blood stem cell harvest allowing a more rapid engraftment and shorter hospital stays. From its initial experimental applications in the leukemias, this approach has been used increasingly widely in diseases such as the lymphomas and germ cell tumor. In the hematological malignancies and lymphomas, there is clear evidence that this approach can salvage patients who would otherwise die from their disease with conventional dose chemotherapy (22). An initial experience of using etoposide, carboplatin and cyclophosphomide in salvaging patients with lapsed germ cell tumours with chemosensitive disease, indicated that between 30-40% of these patients would attain long remissions (23). In the last 20 years, we have added paclitaxel to the previous three drugs, and for patients with ciplatinum-sensitive, disease, our results indicate that about 70% of these patients are achieving remissions with this approach (24).

It might be anticipated that this technique would be appropriate for patients with high-risk GTN. We have previously attempted high dose in 15 cases in the UK over the last 15 years but at this time only 2 appeared to have become long-term survivors (25). A more recent analysis has shown somewhat better results with 8 of 25 patients achieving remission (unpublished). So why has this approach not been more successful? Part of the problem likely resides in the fact that high dose is kept as a last line of attack after multiple other therapeutic strategies have failed including several lines of prior chemotherapy.

However, other possibilities for poor results also need to be considered. Thus, at least some patients receiving high dose chemotherapy for presumed GTN may not in fact have a gestational tumor at all. In Fig. 25.1 is a patient who had a widely metastatic tumor with an apparent primary in the uterus.
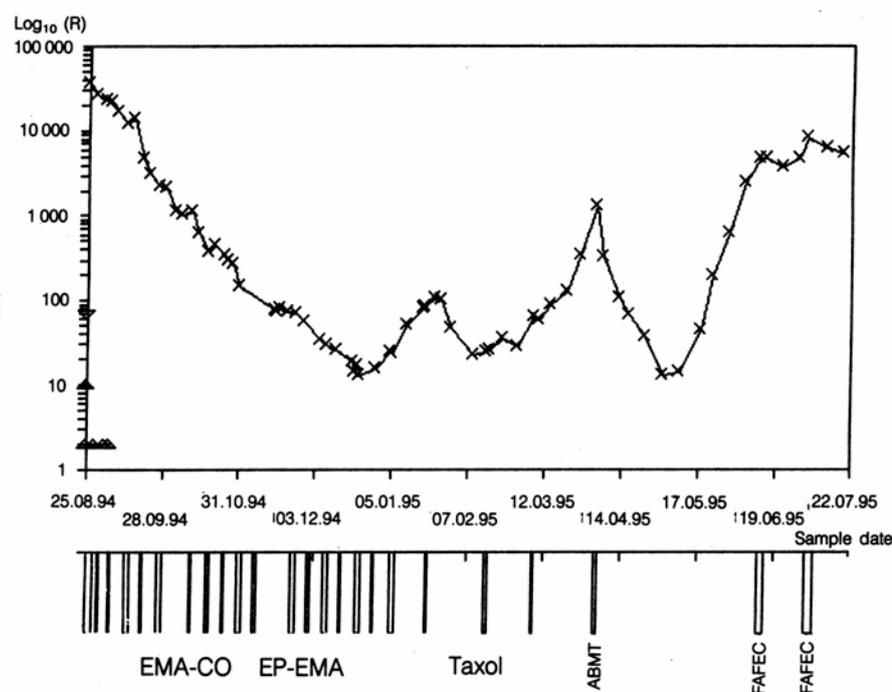

Figure 25.1 Patient presenting with widely metastatic disease involving the uterus, lungs and brain. Histology of necrotic tumor from the brain was compatible with choriocarcinoma but on molecular genetic analysis no paternal genes were detectable. After an initially good response to chemotherapy her disease became progressively more drug resistant to Taxol and had only a brief response to high-dose chemotherapy (etoposide, carboplatin and cyclophosphamide).

Morphological choriocarcinoma was removed with the cranial metastasis but this highly necrotic tumor did not contain detectable paternal genes. In this patient's case it is possible that she did not have a gestational tumor and the brevity of the response to high-dose chemotherapy is clearly very disappointing. It is clear that further experience needs to be obtained using this approach in patients who have gestational rather than non-gestational trophoblastic tumors and perhaps earlier in their treatment (for example in high risk patients who fail their first salvage treatment). Moreover, it has become clear in other tumour types that giving high dose as a tandem or even triple procedure appears better than using it only once. If high dose therapy is going to be considered it is important that it is not reserved until the patient is moribund with drug-resistant tumor and it is probably best to give it at least as a tandem transplant.

25.8   EXPERIENCE WITH NEW AGENTS

At present we have two single drugs, methotrexate plus folinic acid (MTX/FA) and actinomycin D (ActD) with treatment schedules that are clearly effective in patients with low-risk GTN. Whilst there is a continued debate as to which drug and schedule can achieve the best primary remission rate with the least toxicity, a proportion of patients will develop resistance to either agent. In the case of methotrexate and folinic acid, swapping to the other single agent ActD when the hCG level is ≤300 IU/L will cure most. However, a few will develop resistance to ActD and those who become resistant to MTX treatment with an hCG > 300IU/L require combined agent chemotherapy, though an alternative approach using single agent carboplatin is being piloted in Sheffield The idea here is to start with the least toxic therapy first as the overall cure rate is approaching 100%. Indeed, patients receiving combination chemotherapy do have to accept both the short-term side effects of more intensive chemotherapy such as reversible alopecia and myelosuppression, and the more worrying long-term safety profile of combination chemotherapy. As discussed in Chapter [24], these patients have to accept that there is a small long-term penalty in terms of an earlier menopause and potential second tumor induction. At present the balance of risks is clearly in favor of intensive chemotherapy since the risks of the patient's primary disease far outweigh the long-term risks of intensive chemotherapy. However, the increasing data on the incidence of acute myeloid leukemia in patients receiving etoposide (26) indicate that this drug should only be used in patients with disease that has become resistant to methotrexate or in high-risk patients from the outset. The duration of chemotherapy may be important in increasing the risk of inducing acute myeloid leukemia. Provided treatment can be kept shorter than 6 months, and preferably shorter than 5 months, we have not seen a case of acute myeloid leukemia in patients with GTN in the last 22 years. Moreover, the latest analysis in more than 30,000 patients years of follow-up shows there is a reduction in risk of several cancers including breast and lung cancer. Therefore the overall risk of a second cancer in patients treated with EMA/CO is in fact zero compared to the general age matched untreated population (27)) and since we have shortened the duration of treatment. Nevertheless, we do need to develop new chemotherapeutic agents that (i) hopefully have a better long-term safety profile and (ii) have activity against GTN that have become resistant to currently established agents.

In the past 20 years regimens containing the taxane, paclitaxel along with new anti-metabolites gemcitabine, pemetrexed and capecitabine have been shown to have activity in managing GTN (28) Indeed, paclitaxel combined with etoposide alternating two weekly with paclitaxel and cisplatin (TE/TP) (29) salvages 75% of patients failing EMA/CO and is considerably less toxic than EP/EMA and so a randomised trial to compare these regimens is required. However, there are many new molecularly targeted therapies that have been developed which could be relevant to the treatment of GTN. A

comprehensive list of these is beyond the scope of this chapter but a few of these novel agents are listed in Table 25.1.

Table 25.1 Anticancer compounds in development and of potential major clinical interest

Growth Factor, cell signaling and kinase inhibitors	Epidermal growth factor eg. gefitinib, erlotinib, Vascular endothelial growth factor e.g. bevacizumab, Fibroblast growth factor eg. AZD4547 Multi-targeted kinase inhibitors eg sunitinib, sorafenib mTOR eg everolimus Cell cycle targets eg aurora, polo-like kinase, CDK7, CHK1 and WEE1 inhibitors
Immune therapies	IDO inhibitors, anti CTLA4 (ipilimumab) and anti-PDL-1(nivolumab) antibodies

There is a tremendous amount of work going on developing growth factor receptor and intracellular signaling molecule antagonists to try and produce more specific and less toxic agents (30). A number of tumors have been shown to for example over-express normal or mutated versions of the epidermal growth factor receptor (EGFR). Several orally bioavailable small molecule inhibitors to EGFR are now in widespread clinical use including erlotinib, gefitinib and afatinib (31). For example erlotinib is licensed for use in non-small cell lung cancer. Interestingly, there is evidence that some GTN over-express EGFR although it's role in promoting tumourigensis in this disease setting is unclear . We have now tried gefitinib and erlotinib in several drug-resistant cases of GTN where the EGFR was seen to be highly expressed and so far not seen any response. Inhibitors of vascular endothelial growth factor, such as bevacizumab, are potentially very promising. We have seen very transient responses to bevacizumab in two drug resistant cases of GTN. This and other antiangiogenic

compounds, need evaluation in GTN. What is particularly interesting with this class of agent is that when combined with chemotherapy, they re-sensitise resistant tumors to cytotoxic chemotherapy; therefore their role is likely to be in combination with cytotoxic agents.

In addition, there is a vast new array of small molecule inhibitors to other intracellular cell signaling molecules which may serve as points of convergence in growth factor action. For example mTOR is a kinase crucial for mediating the proliferative effects of many different growth factors as well as being an important energy sensor (32). Several new inhibitors which block mTOR function including everolimus are now in advanced clinical development in common tumour types. Interestingly, they already have clear activity in renal cancer a disease where little progress has been made over many years. Multi-targeted kinase inhibitors have also been generated, which as their name implies, disrupt the activity of several molecules. Sorafinib and sunitinib are good examples of this type of inhibitor. Although 'dirty' in their action they nevertheless appear to be well tolerated like many of the other cell signaling inhibitors and are also active in renal cancer.

With modern high throughput chemistry it is now possible to make small molecule inhibitors to just about any kinase. There are over 600 kinases in the human kinome so choosing which ones to target is important. Another obvious area are the kinases which regulate the cell cycle and amongst these CDK7 and CHK1 appear to be promising new targets for cancer therapies (33, 34). However, their role like so many other drugs including some of the older style agents such as oxaliplatin and temozolamide is yet to be defined in GTN.

Targeting cancer cells by exploiting specific antigens expressed on the tumor cell surface has been a long-term hope and aim for oncologists. GTN in common with all pregnancies express a wealth of foreign paternal genes which would normally trigger a vigorous immune response in the female patient. However, this is suppressed through a variety of mechanisms so that the pregnancy is not rejected. Interestingly several new immune modulating agents have been developed. Amongst these are anti-CTLA4 and PDL1 antibodies such as ipilimumab and nivolumab, respectively. These agents have already shown considerable promise in breaking the immune tolerance exhibited by other cancer types (35, 36) so there is now a need to test them in GTN resistant to current therapies. Obviously, hCG production by the tumour might be another potential target as long as the hCG is present on the tumour surface. Animal data suggest that anti-hCG antibody therapy or vaccine based therapy might provide an alternative therapeutic strategy. One method of amplifying this therapeutic concept is antibody-directed enzyme prodrug therapy (ADEPT). If the active form of the prodrug has a very short half-life, then specific enzymatic activation of the prodrug on the tumor cell surface might increase the therapeutic index sharply. This approach is complex and continues in development but it has been shown to be active in choriocarcinoma xenografts experimentally (37, 38).

The number of agents shown in Table 25.1 is far from exhaustive

and it is likely that we will have other active compounds to assess in the gestational tumors in the coming decade. Clearly, however, the long-term safety profile of any new agent will not be available for many decades to come. It is therefore imperative that patients receiving novel and hopefully successful therapies are followed up for life so that any late side effects from their treatment can be evaluated. Only in this way will it be possible to reassure future generations of women receiving this treatment that there is a satisfactory balance of risk between their primary disease and the late side effects of the therapy that is being recommended.

25.9   OTHER POTENTIAL THERAPEUTIC TARGETS

GTDs are rare diseases and their diagnosis may not require histological verification. Tissue for molecular and cell-biology studies is therefore in limited supply. Never-the-less the main conclusion from such studies is that after neoplastic transformation of cytotrophoblast stem cells, specific differentiation programmes dictate the type of tumour that develops. Such studies have also confirmed distinct pathogenesis in complete and partial moles, though the molecular aetiology underlying the development of molar pregnancy remains obscure (39). In the small but significant proportion of patients with GTN who develop resistant or recurrent disease it may be possible to design target based treatments to inactivate molecular pathways that are essential for tumour cell growth and survival. Activation and over-expression of the c-MYC oncogene is frequent in human cancers, GTN being no exception. Targeting strategies might include – inactivation of c-MYC function and expression, disrupting MYC-MAX interaction, blocking the function of c-MYC regulated genes and using antisense oligonucleotides to silence c-MYC expression. Other molecular targets include EGFR (a transmembrane-receptor tyrosine kinase over-expressed in many epithelial tumours including those of trophoblastic tissue), mitogen-activated proteininase (MAKP), mammalian target of rapamycin (mTOR) and matrix metalloprotein (MMP).

25.10 COST EFFECTIVENESS OF CENTERS TREATING GTD AND GTN

Medical advances have improved the clinical management options available, but these together with demographic changes and the rise of expectations of a more health-conscious public are placing increasing demands on limited resources. Economic evaluation (value analysis) is therefore likely to assume increasing importance even with curable cancers such as GTN. In drawing up contracts, commissioners (be

they patients or their agents) are still uncertain as to what they should demand to achieve the best quality and most cost-effective care. The onus is on the expert provider to advise them of up-to-date practice in sensible terms. For example, it will be important to prove prospectively that specialist centers are essential to monitor and treat GTD/GTN. In less developed countries, where resources are scarce, the case for the provision of funds to care for these rare diseases will be difficult to justify unless cost effectiveness can be unequivocally demonstrated.

Whereas with palliative therapy there is an acknowledged lack of outcome measures, it is not difficult to establish the cost utility of treatment used in curing cancer. Health economists in the USA demonstrated that the successful treatment of teratoma in one year produced sufficient economic benefit to support all the drug development costs of the preceding 17 years of the National Cancer Institute's program (40). Also, we estimated (41) that the average cost of treating a patient with high-grade non-Hodgkin's lymphoma is no greater than £6000 (US $9000); the cost per life year saved on such patients is about £1000 (US $1500). In undertaking such calculations it is mandatory to include factors other than the cost of the chemotherapeutic agents; these will include time and other materials (including nursing/medical resources), and must take into account supporting investigations, outpatient and particularly in-patient care, as well as the 'hidden' costs such as hospital overheads, including an allowance for capital depreciation. In one model we have derived it is possible to break down the overall costs of treating particular cancers into individual treatment categories with recognized outcomes. It is then relatively easy to obtain real data on consumption of cytotoxic and supportive drugs by individual disease groups, as well as the investigations undertaken, and to combine these with an agreed estimate of the costs of in-patient stay and out-patients visits. These can then be added together to gain an overall assessment of average costs of care. The value of a course of chemotherapy to a patient with cancer may be displayed best by calculating the number of months or years of benefit that the treatment will provide; with curable tumors treatment cost can then be justified in terms of extended life (survival costs), i.e. by cost per unit of survival time. With GTNs which are highly chemosensitive, good-quality normal life expectancy in excess of 95% for patients of childbearing age can be expected. In the mid 1990s the average basic cost for treating such a patient was £5000 (US $7500), thus the cost per life year saved was less than £200 (US $300) (42)
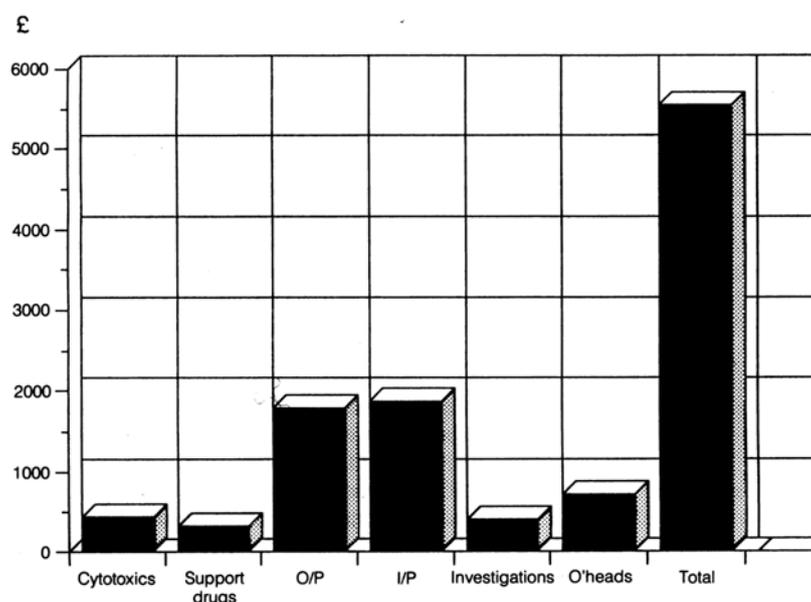
Table 22.2 Approximate average costs of curative chemotherapy for gestational trophoblastic neoplasms: O/P, outpatient attendances; I/P, inpatient stays; O'heads, hospital overheads. Costs from 1993.

However, to offer comprehensive screening and monitoring facilities for GTD, as well as providing expert treatment, centers need more than just clinical staff and chemotherapeutic drugs. State-of-the-art information technology, expert computer technologists, a knowledgeable administrator with good secretarial back-up, and appropriate clinical chemistry (for accurate and well-interpreted hCG data) are all requirements that have to be built into the total cost to be charged for the service. In the UK the national service costs the Department of Health £2.5m per annum. Each year all cases of GTD are registered and followed in case of persistent disease requiring further intervention. When rarer and more difficult-to-treat tumours (for example PSTT or ETT) are excluded the cure rate for GTN approaches 100% and most of these women have normal reproductive lives. In 2012 over 1,800 cases were registered with the UK Trophoblast Centres, 154 requiring further intervention (chemotherapy/surgery). The cost per quality adjusted life year (QALY) saved is therefore estimated to be less than £GB 500 ($US 750). Thus a co-ordinated system for the identification and treatment of gestational trophoblastic disease must rank as one of the most cost-effective health care strategies presently available.

What are the changes for the future that are most likely to affect the balance of the cost-benefit equation?

Certainly there is likely to be a trend towards more out-patient or

even domiciliary care - with better quality of life and less expense for patients, but with problems of effective supervision by the center.

New drugs and techniques are likely to make a significant impact on health care budgets. However, when evaluating the case for these it is important to assess the benefits in both clinical and monetary terms since decisions based solely on purchase costs may ignore advantages which in the long term may outweigh the initial price disadvantage. They must therefore be properly researched, with incorporation of economic evaluation as well as the standard clinical and quality measures.

With small numbers of patients being treated (even in specialist centers) the role of clinical trials is likely to increase. There should be more cross-center collaboration since it has been shown that multi-center controlled clinical trials, probably by standardization of treatment, often in collaboration with specialist centers, offer higher survival rates, particularly for less common cancers (43). In addition, patients are generally willing to take part in such studies (44). Funding of such clinical research must therefore remain a high priority.

Long-term management and sequelae must be taken into account in assessing global costs and benefits. The future is bright for patients with GTD; they can be cured by appropriate chemotherapy given under expert supervision. They are likely to lead productive lives, to remain fertile, and to be free of major long-term physical effects. However, both the short- and the long-term psychological trauma of having a potentially, life-threatening illness requiring sometimes acutely toxic chemotherapy must not be underestimated; there may be a role for ongoing counselling or even personal rather than remote computerized follow-up.

25.11 CONCLUSION

We can conclude, therefore, that there is a good case for registration and monitoring of all cases of GTD through specifically designated screening centres staffed by expert clinicians to ensure the almost 100% success that we see that it is possible to achieve in the treatment of these patients (28, 45).

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