

FUTURE PROSPECTS

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22.1 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 tumors (GTT) 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 GTT needs the following elements:

1. registration of patients with or at risk of GTD or GTT, 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 management of the patients and their 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.

22.2 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 GTT. This could explain the clinically observed phenomenon that the abnormal trophoblast in GTD and GTT never 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 GTT. This is because hCG exists in a number of hCG β immunoreactive forms. Regular hCG, hyperglycosylated hCG, nicked hCG, hyperglycosylated and 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 GTT cases. The same molecules and β -subunit core fragment 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 GTT, prior to or following therapy, or during a recurrence.

As emphasized in Chapter 5, assays can underestimate or miss GTD and GTT. At present the recommendation for an hCG assay for screening, monitoring and following up patients with GTD and GTT 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 GTT by the profile of the

proportion of hCG and its metabolic degradation products that are produced.

Indeed, recent 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). 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 GTT 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 assays for hCG have allotted an upper limit of normal of 5 U/l. It is not all that rare for some patients to have values in the range of 5—50 U/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 (3); 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 (4).

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 (5) but the full implications of this on clinical outcome require further investigation. The emerging role of hyperglycosylated hCG in this and other clinical situations is discussed in Chapter 5.

22.3 MOLECULAR GENETICS

Our understanding of the molecular genetics of GTD and GTT 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 GTT. In the future it will be important to identify what this mechanism or mechanisms are, both to understand the disease process better and to understand the process which makes gestational tumors so much more chemosensitive than the majority of the more common human cancers. At present we do not understand 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 (6). Affected individuals appear to nearly always have molar pregnancies. The function of the normal gene and the affect of the mutations is unknown. Since 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. The latter point is important as it means we are currently uncertain whether IVF using donor eggs will help affected women to achieve a normal pregnancy.

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 GTT 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 and an androgenetic complete molar pregnancy.

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 (7). 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.

22.4 MOLECULAR BIOLOGY

With the identification of NLRP7 as a key gene involved in the development of recurrent bi-parental CHM there is now an urgent

need to understand how the corresponding protein works. Unfortunately knock-out studies in mice are not possible as these animals lack an equivalent gene which might explain why this disease is not seen in these animals. Consequently, alternative strategies are required including RNAi-mediated knockdown in model cell systems and molecular modeling/bio-informatic based studies. Once we understand how this gene functions in health and disease we may be able to extrapolate the findings to other GTD settings where mutations in NLRP7 itself 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 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 (8). Increased expression of p53 gene and c-fms has been reported in complete molar pregnancy (9,10). 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 (11,12). 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.

22.5 OMIC TECHNOLOGIES IN GTD RESEARCH

The advent of high through-put screens using geneomic, proteomic, metabonomic 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 hoped that the next 10 years should see several exciting developments in this area.

22.6 INTENSIVE CARE FOR PATIENTS PRESENTING WITH ADVANCED DISEASE

Patients with organ failure from GTD or GTT 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 GTT 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. 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 GTT 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 GTT is the liver. Extensive intrahepatic metastases which can hemorrhage can

result in hepatic failure and major clotting problems. Provided the patient can be supported through the acute phase, recovery of liver function will occur as the tumor comes under control. However, it should be recognized that the presence of liver metastases in a patient with GTT continues to be a significant adverse prognostic factor.

22.7 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 (13). An initial experience of using etoposide, carboplatin and cyclophosphamide in salvaging patients with lapsed germ cell tumours with chemosensitive disease, indicated that between 30-40% of these patients would attain long remissions (14). In the last 12 years, we have added paclitaxel to the previous three drugs, and for patients with cisplatin-sensitive, disease, our current results indicate that about 70% of these patients are achieving remissions with this approach (15).

It might be anticipated that this technique would be appropriate for patients with high-risk GTN. We have attempted high dose in 15 cases in the UK over the last 15 years but so far only 2 appear to have become long-term survivors (16). So why has this approach not been very 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. 22.1 is a patient who had a widely metastatic tumor with an apparent primary in the uterus.

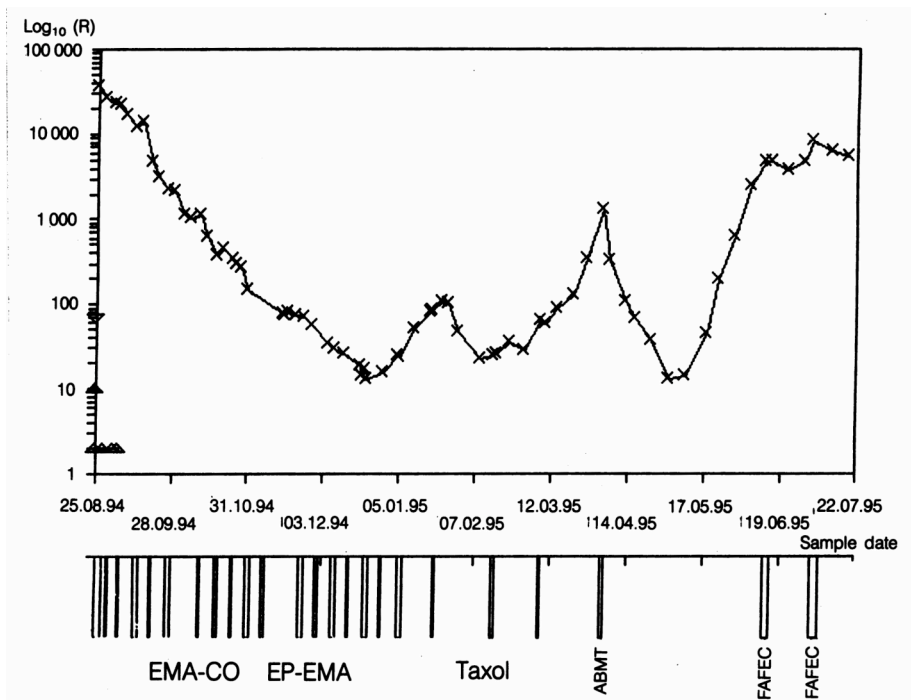


Figure 22.1 Patient presenting with widely metastatic disease involving the uterus, lungs and brain. Histology of necrotic tumor from the brain was compatible with choriocarcinoma but on molecular genetic analysis no paternal genes were detectable. After an initially good response to chemotherapy her disease became progressively more drug resistant to Taxol and had only a brief response to 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). 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.

22.8 DEVELOPMENTS IN CHEMOTHERAPY FOR GTD AND GTT

At present we have a drug and treatment schedule with methotrexate and folinic acid that is clearly effective in patients with low-risk

GTD and GTT which has an acceptable toxicity profile both short and long term. However, 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 [], these patients have to accept that there is a small long-term penalty in terms of 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(17) 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 GTT in the last 12 years since we have shortened the duration of treatment. The incidence of second tumors following more intensive chemotherapy clearly confirms that we need to develop new chemotherapeutic agents that (i) hopefully have a better long-term safety profile and (ii) have activity against GTD and GTT that have become resistant to currently established agents.

At present there is considerable excitement in medical oncology about the potential of a range of new anticancer agents that are coming through to the clinic. Some of these agents are shown in Table 22.1. The taxanes, paclitaxel and docetaxel, are thought to act primarily by promoting the polymerization of tubulin and are recognized to be active in a broad range of tumour types. We and others have shown activity of paclitaxel in germ cell tumours and GTN. Indeed, paclitaxel combined with etoposide alternating two weekly with paclitaxel and cisplatin salvages 70% of patients failing EMA/CO and is considerably less toxic than EP/EMA our current regimen for patients relapsing after EMA/CO (18).

Table 22.1 Anticancer compounds in development and of potential major clinical interest

Taxanes	Taxol (paclitaxel) Taxotere (docetaxel)
Camptothecins	Topotecan Irinotecan
Antimetabolites	Fludarabine 2-Chlorodeoxyadenosine Gemcitabine Tomudex (raltitrexid) Capecitabine Pemetrexed
Growth Factor, cell signaling and kinase inhibitors	Epidermal growth factor eg. gefitinib, erlotinib, Vascular endothelial growth factor e.g. bevacizumab, Fibroblast growth factor eg. SU6668 Multi-targeted kinase inhibitors eg sunitinib, sorafenib mTOR eg RAD001, CCI779 Cell cycle targets eg aurora and polo-like kinase inhibitors
Miscellaneous	Mixed amine-platinum complexes e.g, oxaliplatin temozolomide

The camptothecins, topotecan and irinotecan, are also promising compounds with a new mechanism of action. In contrast to drugs such as etoposide, which inhibit topoisomerase II, the camptothecins inhibit topoisomerase I. Both these compounds have been shown to have significant antitumor activity against quite a wide range of cancers and, as they become available, need to be assessed in GTD and GTT.

A new generation of antimetabolites has been coming into the clinic and fludarabine and 2-chlorodeoxyadenosine have significant activity against hematological and lymphoid malignancies. Gemcitabine particularly when combined with cisplatin has

activity against a wide range of solid tumors. Gemcitabine clearly has activity in drug resistant GTT when combined with cisplatin. Tomudex, a thymidylate synthetase inhibitor has activity in solid tumors but has yet to be evaluated in patients with drug resistant GTT. Similarly the multi-targeted anti-folate drug pemetrexid is also active.

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 (19). 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 lapatinib (20). 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 tumourigenesis 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 or Zactima, are potentially very promising. We have seen transient responses to bevacizumab in two drug resistant cases of GTN. This and other antiangiogenic compounds in development such as the fibroblast growth factor inhibitors, (eg SU6668), 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 (21). Several new inhibitors which block mTOR function including RAD001 and CCI779 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 the aurora and polo-like kinases appear to be promising new targets for cancer therapies. 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. Obviously, hCG production by the tumour might be one potential target as long as the hCG is present on the tumour surface. Animal data suggest that ant-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 (22,23).

The number of agents shown in Table 22.1 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.

22.9 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 (24). 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 inactive 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).

22.10 COST EFFECTIVENESS OF CENTERS TREATING GTD AND GTT

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 GTD. 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. 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 (25). Likewise, we have estimated (26) 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 GTT 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) (27) (Figure 22.2).

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) are excluded the cure rate approaches 100% and most of these women have normal reproductive lives. In 2006 over 1,500 cases were registered with the UK Trophoblast Centres, 144 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.

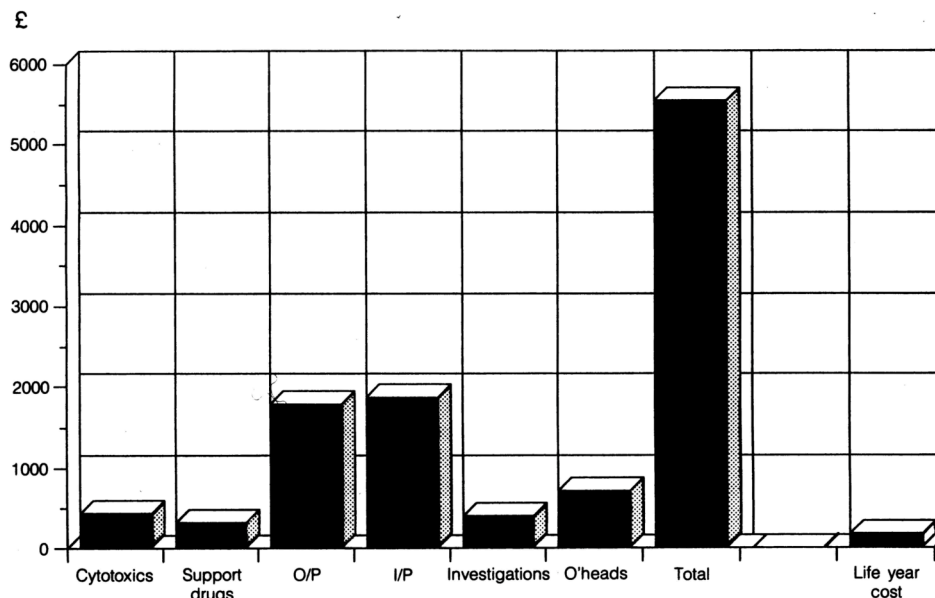


Table 22.2 Approximate average costs of curative chemotherapy for gestational trophoblastic tumors: O/P, outpatient attendances; I/P, inpatient stays; O'heads, hospital overheads.

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[28]. In addition, patients are generally willing to take part in such studies[29]. 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.

22.11 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 (30).

REFERENCES

1. Cole LA, Khanlian SA, Muller CY, Giddings A, Kohorn E, Berkowitz R. (2006) Gestational trophoblastic diseases: 3. Human chorionic gonadotropin-free beta-subunit, a reliable marker of placental site trophoblastic tumours. *Gynecol Oncol* 102(2):160-4.
2. Cole LA, Butler SA, Khanilian SA, Giddings A, Muller CY, Seckl MJ et al. (2006) Gestational trophoblastic diseases: 2. Hyperglycosylated hCG as a reliable marker of active neoplasia. *Gynecol Oncol* 102(2):151-9.
3. Palmieri C, Dhillon T, Fisher RA et al. (2007) Management and outcome of healthy women with persistently elevated beta-hCG. *Gynecol Oncol* 106:35-43.
4. Cole LA, Sasaki Y, Muller CY. (2007) Normal production of human chorionic gonadotropin in menopause. *N Engl J Med* 356:1184-1186.
5. Mitchell H, Seckl MJ. (2007) Discrepancies between commercially available immunoassays in the detection of tumour-derived hCG. *Mol Cell Endocrinol* 2;260-262:310-3.
6. Murdoch S, Djuric U, Mazhar B, Seoud M, Khan R, Kuick R, et al. (2006) Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. *Nat Genet* 38(3):300-2.

7. Fisher RA, Savage PM, MacDermott C, Hook J, Sebire NJ, Lindsay I, et al. (2007) The impact of molecular genetic diagnosis on the management of women with hCG-producing malignancies. *Gynecol Oncol* 107(3):413-9.
8. Tuncer ZS, Vegh GL, Fulop V, Genest DR, Mok SC, Berkowitz RS. (2000) Expression of epidermal growth factor receptor-related family products in gestational trophoblastic diseases and normal placenta and its relationship with development of postmolar tumor. *Gynecol Oncol* 77(3):389-93.
9. Cheung AN, Srivastava G, Pittaluga S, Man TK, Ngan H, Collins RJ. (1993) Expression of c-myc and c-fms oncogenes in trophoblastic cells in hydatidiform mole and normal human placenta. *J Clin Pathol.* 46(3):204-7.
10. Cheung AN, Srivastava G, Chung LP, Ngan HY, Man TK, Liu YT, et al. (1994) Expression of the p53 gene in trophoblastic cells in hydatidiform moles and normal human placentas. *J Reprod Med* 39(3):223-7.
11. Sarkar S, Kacinski BM, Kohorn EI, Merino MJ, Carter D, Blakemore KJ. (1986) Demonstration of myc and ras oncogene expression by hybridization in situ in hydatidiform mole and in the BeWo choriocarcinoma cell line. *Am J Obstet Gynecol.* 154(2):390-3.
12. Fujino T. (1987) Analysis of c-onc genes in choriocarcinoma cells. *Hokkaido Igaku Zasshi.* 62(5):798-807.
13. Armitage JO. (1994) Bone marrow transplantation. *N Engl J Med* 330(12):827-38.
14. Lotz JP, Andre T, Donsimoni R, Firmin C, Bouleuc C, Bonnak H, et al. (1995) High dose chemotherapy with ifosfamide, carboplatin, and etoposide combined with autologous bone marrow transplantation for the treatment of poor-prognosis germ cell tumors and metastatic trophoblastic disease in adults. *Cancer* 75(3):874-85.
15. McNeish IA, Kanfer EJ, Haynes R, Giles C, Harland SJ, Driver D, et al. (2004) Paclitaxel-containing high-dose chemotherapy for relapsed or refractory testicular germ cell tumours. *Br J Cancer* 90(6):1169-75.
16. El-Helw LM, Seckl MJ, Haynes R, Evans LS, Lorigan PC, Long J, et al. (2005) High-dose chemotherapy and peripheral blood stem cell support in refractory gestational trophoblastic neoplasia. *Br J Cancer* 93(6):620-1.
17. Boshoff C, Begent RH, Oliver RT, Rustin GJ, Newlands ES, Andrews R, et al. (1995) Secondary tumours following etoposide containing therapy for germ cell cancer. *Ann Oncol* 6:35-40.
18. Wang J, Short D, Sebire NJ, Lindsay I, Newlands ES, Schmid P, et al. (2008) Salvage chemotherapy of relapsed or high-risk

- gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol* May 2.
19. Petrelli A, Giordano S. (2008) From single- to multi-target drugs in cancer therapy: when aspecificity becomes an advantage. *Curr Med Chem* 15(5):422-32.
 20. Ciardiello F, Tortora G. (2008) EGFR antagonists in cancer treatment. *N Engl J Med* 358(11):1160-74.
 21. Settleman J, Kurie JM. (2007) Drugging the bad "AKT-TOR" to overcome TKI-resistant lung cancer. *Cancer Cell* 12(1):6-8.
 22. Springer CJ, Bagshawe KD, Sharma SK, Searle F, Boden JA, Antoniow P, et al. (1991) Ablation of human choriocarcinoma xenografts in nude mice by antibody-directed enzyme prodrug therapy (ADEPT) with three novel compounds. *Eur J Cancer* 27(11):1361-6.
 23. Bagshawe KD. (1993) Antibody-directed enzyme prodrug therapy (ADEPT). *Adv Pharmacol* 24:99-121.
 24. Shih LM. (2007) Gestational trophoblastic neoplasia - pathogenesis and potential therapeutic targets. *Lancet Oncol* 8:642-50.
 25. Shibley L, Brown M, Schuttinga J, Rothenberg M, Whalen J. (1990) Cisplatin-based combination chemotherapy in the treatment of advanced-stage testicular cancer: cost-benefit analysis. *J Natl Cancer Inst* 7;82(3):186-92.
 26. Hancock BW, Baber A. (1995) The cost effectiveness of cancer chemotherapy: a clinicians view. *Proc R Coll Phys Edinburgh*. 25:61-6.
 27. Smith SC, Sheridan E, Dorreen MS, Hancock BW. (1993) Gestational trophoblastic diseases-rare but curable at low cost: contemporary experience of the Sheffield Supraregional Screening and Treatment Centre. *Br J Cancer* 67(Supp 20):30.
 28. Stiller CA. (1994) Centralised treatment, entry to trials and survival. *Br J Cancer* 70(2):352-62.
 29. Slevin M, Mossman J, Bowling A, Leonard R, Steward W, Harper P, et al. (1995) Volunteers or victims: patients' views of randomised cancer clinical trials. *Br J Cancer* 71(6):1270-4.
 30. El-Helw LM, Hancock BW. (2007) Treatment of metastatic gestational trophoblastic neoplasia. *Lancet Oncol* 8(8):715-24.