THE PRESENT AND FUTURE MANAGEMENT OF MALIGNANT BRAIN TUMOURS: SURGERY, RADIOTHERAPY, CHEMOTHERAPY

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While the majority of malignant brain tumours remain ultimately incurable, a variety of intermediate outcomes is nevertheless possible, depending on histological tumour type and grade. A common treatment strategy obtains for most malignant brain tumours. Surgery followed by radiotherapy are the major treatment modalities, while chemotherapy provides adjuvant and palliative support. The most exciting areas of advance lie in the genetic targeting of conventional treatments and in applying biotherapies and agents specifically directed at molecular targets within the cell. We describe the current status and future prospects for each of these modalities.

SURGERY

Gliomas are the most frequently diagnosed class of primary malignant brain tumour. Since these tumours are incurable, the main emphasis is on symptom alleviation and prolongation of survival. In this context, neurosurgery has the distinct but interrelated aims of providing histological diagnosis, cytoreduction, symptomatic relief, and local delivery of adjuvant therapy.[1][2] The surgical principles used in managing other malignant tumours are similar, though in some— for example, medulloblastoma—extensive cytoreduction may contribute to cure.

Histological diagnosis

In the great majority of cases of patients with newly diagnosed brain tumour it is imperative to obtain a precise histological diagnosis. Guidance on prognosis, decisions on further management and patient counselling will depend on the histological type and grade of the lesion. It is important to ensure that the tissue samples on which the final diagnosis is based are as representative as possible of the tumour as a whole. The diagnostic accuracy of various biopsy procedures depends on the amount of tissue obtained and the accurate targeting of areas of high diagnostic yield. This can be achieved from an open biopsy or by a radiologically guided, stereotactic procedure.

To acquire a stereotactic biopsy a rigid frame is attached to the patient's head as an external co-ordinate reference system. Various imaging modalities (mainly computed tomography (CT) but also magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT)) can be integrated to produce biopsy target coordinates. This technique presently represents the "gold standard" as it combines accuracy with a relatively low morbidity. Diagnostic pitfalls remain in tumours with pronounced heterogeneity or where small foci of high grade transformation exist in the background of a largely low grade lesion. In such cases, consideration should be given either to acquiring several target coordinates from various areas or to employing a more extensive approach, such as craniotomy and open biopsy.

Cytoreduction

A number of non-randomised studies and one prospective trial have shown improved survival in patients undergoing craniotomy and resection as compared with those having a biopsy only. However, whether the surgery is responsible for this improvement remains unclear. A retrospective audit of survival in 299 patients with newly diagnosed glioblastoma multiforme over the last five years at our institution has shown median survivals of 20, 38, and 53 weeks for patients undergoing biopsy, tumour debulking, and macroscopic resection, respectively. These figures correlate well with a recent publication from the glioma outcome project in the USA, which reported median survivals of 21 and 45 weeks for biopsy and craniotomy, respectively, in 413 prospectively recruited patients.

Patients with tumours situated in accessible, non-eloquent brain areas are candidates for an attempt at total macroscopic resection; interpreted as the removal of all visibly abnormal tissue. While this does not represent all tumour cells it does include the regions where tumour growth and neo-angiogenesis have resulted in blood–brain barrier breakdown (enhancement on CT or MRI scan). Attempts have been made to quantify the extent of resection achieved, mainly by

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calculating the proportion of preoperative enhancing tissue remaining in an early (< 72 hours), postoperative MRI scan. A recent study has suggested that survival advantage is observed when > 98% of the enhancing tissue has been excised. Further developments in surgical technology (image guided surgery, intraoperative ultrasound, CT, and MRI), neuroimaging (PET/SPECT, MR spectroscopy, diffusion tensor imaging), and molecular biology (fluorescence/radio-active labelling of tumour cells in situ) are intended to maximise tumour resection while decreasing procedure related morbidity.

Symptomatic relief

Surgery is a highly effective means of reducing elevated intracranial pressure and relieving the local mass effect caused by glioma. Moreover, major tumour decompression will allow prompt reduction of steroid medication, with the avoidance of the side effects produced by their long term use at high doses. The relative ease with which intracranial pressure can be reduced and neurological symptoms alleviated in each case is balanced against the associated risks. Drainage of a cystic lesion or a polar lobe resection, for example, are relatively low risk procedures, which will produce rapid decompression and facilitate a more extensive tumour resection. The decision to operate in this situation is more straightforward than the removal of a diffuse, ill defined lesion close to an ''eloquent'' brain area. Any surgical intervention is tailored to the patient's symptoms, clinical condition and needs, and prognosis, as well as to the requirements of any adjuvant treatments.

''Palliative'' surgery can also be used for patients with high grade glioma (HGG) that has re-grown after primary therapy (fig 1). The decision to operate may be even more difficult and must take into account the patient's performance status, the time interval from initial presentation and first line treatment, and the available treatment options, including clinical trials.

Delivery of adjuvant treatment

The failure of increasingly sophisticated conventional treatments (surgery and radiotherapy) to control HGG demands the development of new therapeutic paradigms. Further, the delivery of drugs and macromolecules to the brain following systemic, intravascular administration is hindered by the existence of the blood–brain barrier (BBB), the heterogeneity of HGG, and the unique environment of the central nervous system (CNS), which cause varied and unpredictable intracerebral drug distribution. Such factors have led investigators to explore loco-regional routes of administration of new and conventional agents.[3]

A consistent theme running through strategies designed to overcome these difficulties has been the attempt to circumvent the BBB by the direct administration of agents into the extravascular spaces of the CNS. Techniques involving neurosurgery have included parenchymal injections, intra-cavitary instillation, slow release polymer implants, and intraventricular or intrathecal administration. The latter two methods, while useful for accessing cerebrospinal fluid (CSF) spaces, are similarly hindered by the presence of a CSF–brain barrier.

Some agents are introduced at the time of surgery for tumour resection while others require the insertion of access devices for subsequent administration. An example of the first approach is the recent introduction of parenchymal

chemotherapy using biodegradable wafers impregnated with a nitrosurea. In a randomised double blind placebo controlled trial, nitrosurea produced a statistically significant improvement in survival for patients with newly diagnosed HGG. The benefit was small, delivering an improvement of only two months in median survival (13.9 months for nitrosurea v 11.6 for placebo). Other chemotherapy agents are currently under investigation using similar technology.

Access devices, such as indwelling catheters and reservoirs, have been used to deliver a variety of antineoplastic agents including radiolabelled monoclonal antibodies, radioisotopes, and drugs, into the resection cavities of HGG. The main limitation of this approach is its reliance on the process of diffusion within brain parenchyma for distribution. This is dependent on the concentration gradient (requiring very high values at the site of administration), the rate of tissue clearance for the particular agent, and the size of the administered molecule—diffusion being inversely proportional to its molecular weight. It can therefore be a very slow process with a limited volume of distribution. This is a major disadvantage when dealing with diffuse CNS disease such as malignant glioma, where neoplastic cells may be centimetres away from the main tumour mass.

A new and very promising approach explores the feasibility of using bulk flow within the brain extracellular fluid (ECF) space for the intracerebral distribution of agents. This method has been called convection enhanced delivery (CED) and involves the placement within the brain parenchyma or tumour substance of one or more catheters that are subsequently connected to continuous infusion pumps. The pumps must be able to deliver the very low infusion rates that are critical for successful fluid ''convection'' within the brain. Rates of infusion greater than a few μl/min will produce backflow along the catheter and loss of pressure, while too low a pressure will lead to failure of delivery. An increasing body of animal and, more recently, human data shows that a much larger volume of distribution is achieved compared to previous delivery methods. CED is now the method of choice in a variety of phase I through phase III clinical trials investigating novel agents in CNS malignancy.

In summary, surgery plays a central role in the initial diagnosis and symptom control in patients with malignant brain tumours. All but the very elderly and the most infirm patients suspected of having a primary brain tumour should be referred for an opinion from a neurosurgeon with a specialist tumour interest. In addition to its conventional role, neurosurgery is playing an increasing role in novel treatment delivery, of which some modalities have shown early promise in the management of these diseases.

RADIOTHERAPY

Radiotherapy can prolong survival in the majority of patients with malignant brain tumours, including high grade gliomas, and may be curative in others—for example, medulloblastomas and germ cell tumours (the management of low grade gliomas is discussed by Whittle, p ii31). Our understanding of which radiotherapeutic treatment to offer to which patient has notably improved in recent years.[4]

Numerous analyses have demonstrated that prognostic factors operate for patients treated for malignant glioma. In particular these include age, performance status, tumour histology, extent of resection, and possibly tumour size. It is possible to combine such factors into a prognostic guide to the value of radiotherapy in a particular situation. Young

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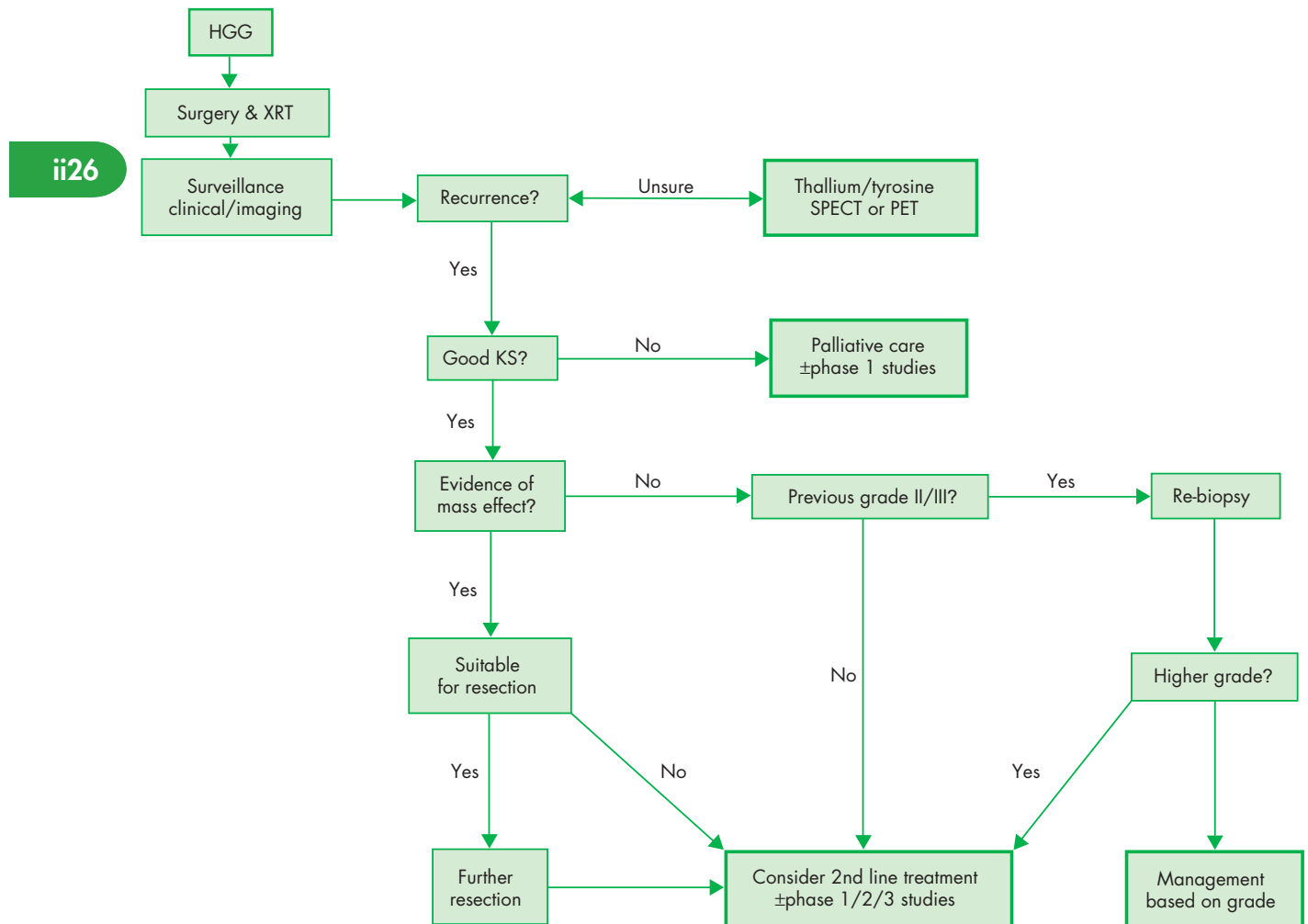
Figure 1 Management algorithm for high grade glioma. HGG, high grade glioma; KS, Karnofsky performance score; PET, positron emission tomography; SPECT, single photon emission computed tomography; XRT, radiotherapy.

patients with good performance scores have a survival prognosis of longer than a year, provided optimal treatment is given. They merit radical treatment with radiation doses of ~ 60 Gy over periods of about six weeks. On the other hand, elderly infirm patients have prognoses of only a few months irrespective of treatment and may be spared radiotherapy altogether. For those with intermediate status, shorter treatment schemes (for example, 30 Gy in two weeks using just six fractions) can bring an appropriate level of survival benefit without overburdening the patient with large numbers of treatment fractions and side effects. Such schemes have gained wide acceptance. It has recently been suggested that age, per se, is not a prognostic factor independent of performance status and that high dose

radiation therapy should be offered to older patients with otherwise good prognostic indicators.

Because high grade glioma cells are widely infiltrating through the oedematous white matter adjacent to tumour, and beyond, it is tempting to use very large radiation fields to cover these cells. However, it has been demonstrated that in spite of wide volume radiotherapy the majority of tumours relapse within 2 cm of the previous tumour's enhancing edge, or the resection cavity. Hence, until this problem is solved radiotherapy to large volumes of brain is not justified. Indeed much attention is currently being focused on using sophisticated radiotherapy planning techniques, including conformal radiotherapy and intensity modulated radiotherapy, to reduce the volumes of ''normal'' brain that are irradiated. This brings with it improvement in the side effects of treatment.

In 1991, the Medical Research Council reported a study in which two doses of radiotherapy (45 Gy *v* 60 Gy) were compared in the treatment of malignant brain tumours. They clearly showed improved survival in those patients receiving the higher dose. This led to the prospect of further benefit from still higher doses. However, dose escalation studies using brachytherapy or stereotactic radiotherapy/radiosurgery have failed to show this improvement. Neither

Surgery: key points

► Tissue diagnosis is necessary for adequate management in the majority of cases
► Surgery may provide prompt symptomatic relief but does not necessarily add to longevity
► Surgery offers prospects for novel treatment delivery

have radiation sensitisers (for example, BudR) nor hypoxic cell sensitisers (for example, tirapazamine) brought any improvement.[4]

The brain is sensitive not only to the total radiation dose but also to the radiation dose per fraction. Numerous attempts have been made at modifying the fractionation schedule for glioma treatment in order to gain therapeutic advantage. However, neither hyperfractionation, accelerated fractionation, hypofractionation, nor any combination of these, has produced any survival advantage.

In view of all of the above, patients with high grade glioma should routinely be offered conventional doses of radiotherapy (60 Gy in 30 fractions over six weeks) without radiation modifiers. Patients with major deficits may be offered shorter courses of treatment, or none, especially if elderly. In any event all patients should receive best supportive care in addition to any radiotherapy.

Whole neuraxis irradiation remains an integral component of curative treatment in patients, particularly children, with tumours such as medulloblastoma that have a propensity for CSF spread. Many of these tumours are also chemosensitive and this modality is used as a means of reducing the overall radiation dose without compromising chance of cure. Although not conclusively backed by randomised trials, this approach has become standard in medulloblastoma. Unfortunately, ependymoma does not seem to respond so well to this approach. Additional late consequences of whole neuraxis treatment include the late effects of irradiating non-neurological tissues such as growing bone and thyroid.

Increasingly chemotherapy is also used to treat germ cell tumours, with radiotherapy confined to treating the primary lesion.[5]

Complications

Radiotherapy is damaging to both tumour and to normal brain, and the potential consequences of treatment must be put in the context of any benefit. The principle acute and intermediate complications are depilation, fatigue, and somnolence and are of greatest concern in patients with short prognoses. Mostly these symptoms are mild and improve with time from irradiation. Of greater concern in patients with long term survival prospects are vascular and white matter change, including necrosis, neuronal fallout, endocrine failure, and second malignancy. Late effects are related to the total delivered dose and the rate of delivery (dose per fraction). While the effects on cognition of large radiation doses are well documented, the effects of lower doses may have been overestimated, particularly if delivered with small fraction sizes.[5]

Radiotherapy for patients with radio-curable tumours such as medulloblastomas or germ cell tumours is quite different. These diseases have a propensity to disseminate throughout the CNS and craniospinal radiotherapy has been directed at this entire target, always using the highest dose that was safely possible.

CHEMOTHERAPY

Chemotherapy has three major roles in cancer: as the primary treatment, as an adjuvant to the primary treatment (to prevent or delay relapse), or as palliative therapy to improve symptoms and prolong survival following primary treatment failure. Some rare neurological conditions such as primary CNS lymphoma, germ cell tumours, and primitive neuroectodermal tumours are chemo-responsive and chemotherapy

> **Radiotherapy: key points**
> ► Radiotherapy can prolong survival in the majority of patients with brain tumours
> ► Application of radiotherapy should be determined by performance and other prognostic factors
> ► Further progress in external beam radiotherapy is likely to come from combination with other treatment modalities

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plays a central role in their management. However, the majority of brain tumours have been considered chemo-resistant and the use of chemotherapy, particularly as adjuvant treatment, is controversial. With the availability of newer drugs and a better understanding of the biology of brain tumours this situation is changing, even for high grade gliomas.[6]

For any chemotherapy agent to be effective it must first penetrate to the cancer and the selective permeability of the BBB poses a particular problem for brain tumours. Some drugs, because of their small molecular size or high lipid solubility, naturally achieve good BBB penetration (nitroso-ureas, temozolomide) and high concentrations in tumour. This can be improved by bypassing the BBB using biodegradable wafers, BBB disruption, or continuous infusion methods. A limited number of drugs, such as methotrexate and cytosine arabinoside, can be given safely by the direct intrathecal route. However, apart from special circumstances, such as childhood acute lymphoblastic leukaemia, they have shown no efficacy in brain tumours.

Chemotherapy for relapsed disease

The nitrosoureas (BCNU, CCNU) have historically played a central role in the chemotherapy of gliomas. However, there are very few studies in which either single agents or combinations are compared and optimum treatment is unclear. By common consent the combination of procarbazine, CCNU, and vincristine (PCV) has been adopted as the "gold standard" in spite of there being relatively little firm evidence for this. PCV has been shown to be more effective than single agent nitrosourea in a prospective randomised study in patients with anaplastic astrocytoma. The same result did not reach statistical significance for patients with glioblastoma. Phase II trials have described response rates to PCV in the region of 20–40% for selected patients with relapsed glioblastoma, though the applicability to the general population may be questioned. Median survival following chemotherapy for relapsed glioblastoma is 3–6 months.

Four to six courses of PCV are usual. Tablets are taken for 10 days with a single intravenous injection every six weeks. The benefits of tumour control must be balanced against the patient's tolerance of the treatment. Though generally well tolerated, the most common side effects are myelosuppression, which may be cumulative, and nausea. Vincristine can cause an uncomfortable polyneuropathy, which usually improves with cessation of the drug. The possible interaction of procarbazine with tyramine containing foods such as red wine and ripe cheese leads to special dietary restrictions. In general, the response to chemotherapy is better in younger patients, with lower grade tumours, good performance status, and longer progression-free interval.

Temozolomide is a new alkylating agent whose activity in patients with relapsed gliomas is similar to PCV. It is given

orally for five days every four weeks and is said to be better tolerated, and associated with a better quality of life, than procarbazine containing regimens. In many countries it is used as primary treatment for relapsed glioma. In the UK, however, it is recommended only for second line use though few patients survive long enough and remain well enough to be considered for it. A prospective, randomised UK national study directly comparing PCV with temozolomide (in two schedules) as first line treatment for high grade glioma at first relapse will assess whether there is a survival or quality of life advantage to the newer treatment. Any benefit will have to be considered against the higher cost of temozolomide.

Other drugs that can be used in patients with relapsed glioma include carboplatin, etoposide, and dibromdulcitol, though their role is not fully established and they are reserved as third line or experimental agents. Among the newer agents the topoisomerase 1 inhibitor, CPT11, has shown promise in some studies, particularly in association with temozolomide.

Differential chemosensitivity in malignant glioma

It has been recognised for some years that there is a differential chemosensitivity among different glioma classes. Recently, however, molecular analysis has appeared to give particular promise as a predictor of response. This leads to the exciting prospect of using molecular biology to improve upon standard pathological methods in directing treatment.

Cairncross and McDonald were the first to show that patients with relapsed anaplastic oligodendrogliomas demonstrated particularly good response to chemotherapy with PCV. Molecular genetic studies then showed that the deletion of the long arm of chromosome 1 and the short arm of chromosome 19 (1p-, 19q-) is common in this group of tumours and, when present, was associated with pronounced chemosensitivity. Indeed patients in these studies enjoyed prolonged remissions, sometimes lasting several years.[7] This chemosensitivity also appears to extend to other dugs such as temozolomide.

While the role of chemotherapy in relapse oligodendroglioma has been clearly established, the value of PCV as treatment adjuvant to radiation is still under study. With optimistic anticipation of the outcome, some workers have postulated that patients suffering from oligodendrogliomas carrying these chromosomal abnormalities may be better served by primary treatment with chemotherapy, reserving radiotherapy for relapse.

In low grade oligodendroglioma, the association of chemosensitivity with LOH1p, 19q status remains, but is not so strong. However, in patients with so called ''oligo-astrocytoma'' the chemosensitivity appears to be predicted by the 1p, 19q status.

It is also clear that anaplastic astrocytoma responds more favourably to chemotherapy than glioblastoma. Further, the genetic changes marking progression of anaplastic astrocytoma to glioblastoma are increasingly understood. While the association of chemosensitivity with the genetic profile is not so well established in malignant astrocytoma, an accurate knowledge of tumour grade is clearly required to allow rational choice of treatment. These findings give real encouragement to search for other molecular markers to improve targeting treatment for individual patients.

Novel delivery methods

Although the BBB is partially disrupted in the vicinity of a brain tumour, it is nevertheless perceived as a barrier to treatment. A variety of methods have been explored to bypass this problem. Neither osmotic BBB disruption, selective BBB opening nor high dose treatment with marrow rescue have shown any survival benefit over conventional treatment. The neurosurgical methods discussed above are, however, showing increasing promise.

Adjuvant chemotherapy

Adjuvant chemotherapy has been successful in some other tumour types (notably breast cancer) in producing durable improvements in survival. Numerous randomised studies have attempted to demonstrate the same effect in patients with brain tumours. The most frequent study design has incorporated nitrosourea based chemotherapy as adjuvant to standard surgery and radiotherapy in comparison to standard treatment alone. Most studies were underpowered and failed to show any survival advantage. In 2002 the glioma meta-analysis trialist group[8] carried out a systematic review of individual patient data from 12 such trials whose data were sufficiently homogeneous for the purpose. Radiotherapy doses ranged from 40–60 Gy and volumes varied from whole brain to tumour only with a margin. All patients received a nitrosourea, some as single agent, others as combination therapy. There was a statistically significant increase in median survival from 10 to 12 months, equivalent to a 6% absolute improvement in survival at one year (from 40% to 46%). This was just sustained at two years but had effectively vanished at three years. The relative benefits were the same for glioblastomas and anaplastic astrocytomas, though clearly due to the shorter life expectancy of the former, the absolute difference was less for this group of patients. Younger, fitter patients seemed to benefit most.

The meta-analysis then clearly demonstrates a statistically significant benefit to adjuvant chemotherapy in high grade gliomas. Should this be adopted therefore as standard practice? Does a 6% improvement in one year survival justify several months of chemotherapy for all patients? An essential difference between this result and that in, say, breast cancer, is that in the latter disease the improvement is durable. It can be argued that offering chemotherapy on progression, when patients have symptoms to palliate, is a better way of preserving a patient's quantity and quality of life. As yet adjuvant therapy has not been accepted as standard-of-care by most clinicians in the UK. However, it can be argued that some young, fit, motivated patients with a good performance status after primary treatment should at least be offered the option of chemotherapy. Further there are encouraging non-randomised data that suggest that temozolomide is much more effective in the adjuvant setting. Results of a European phase III study of adjuvant temozolomide are awaited.

In summary, a significant role for adjuvant chemotherapy in the majority of malignant brain tumours is hard to demonstrate, although in individual histological types such as germ cell tumours or CNS lymphomas benefit is clear. Its major role in the treatment of high grade gliomas remains as a palliative option for recurrent disease with ongoing studies to determine the optimum regimen. With the introduction of molecular genetics as a routine clinical tool in the future, it may become possible to individualise patient care by offering chemotherapy earlier to those in whom there

is a demonstrated abnormality known to confer chemosensitivity, as seems possible for anaplastic oligodendrogliomas.

NEW DIRECTIONS

The outcome for patients with malignant brain tumours following standard treatment is poor and new approaches are needed. The most promising are anti-cancer treatments such as antibodies or small inhibiting molecules, designed against specific molecular targets rather than drugs derived from traditional empiric methods. Thus, for example, angiogenesis inhibitors or signal transduction inhibitors (STI) are designed to target molecules known to be active in particular cancers. In some cancers—for example, breast and lung—drugs, such as traztuzamab and ZD1839 which target the epidermal growth factor receptor, are already entering clinical usage though the results are somewhat mixed. Similar targets exist on gliomas and form the basis of contemporary research.[9]

STI571 (imatinib mesylate) is an oral drug with several actions, including inhibition of tyrosine kinases activated by the platelet derived growth factor receptor (PDGFR). PDGFR, and its ligand PDGF, are frequently expressed in gliomas, and are thought to be important in promoting proliferation. PDGF/R are considered to work in an autocrine loop fashion, stimulating glial cell division. STI571 has demonstrated the ability to inhibit this in vitro in cell lines, and in vivo in animal models. Phase I and II clinical trials of STI571 have already been carried out in other tumours such as chronic myeloid leukaemia and gastrointestinal stromal tumours with encouraging results, and trials are ongoing to investigate its role in glial tumours. Since there are multiple aberrant elements in the cell cycle control of malignant gliomas it is likely that such agents will be needed in combination to be effective in these diseases. This work is in its infancy but has a compelling logic and significant promise.

A number of other highly innovative approaches in oncology have been grouped under the term "biotherapies", indicating their aim to control cancer either by manipulating biological processes or by utilising their products as oncolytic agents. They can be addressed under the headings of gene therapy, immunotherapy, oncolytic viral therapy, and biological toxins; all of which have been applied to neuro-oncology.

Gene therapy

The term "cancer gene therapy" implies the manipulation of the tumour cell genome for therapeutic purposes. It is fair to say that gene therapy has failed to fulfil early expectations, probably because these were set too high. Gene therapy can take on several different strategies:

Suicide gene therapy

Suicide gene therapy involves the incorporation into a tumour cell of a gene whose product, either alone or in combination with another agent, results in cell death. The most widely used paradigm is the introduction of non-human enzymes that are able to convert non-toxic pro-drugs into cytotoxic metabolites. Two enzyme/pro-drug combinations account for the majority of human trials to date:

► Herpes simplex virus type 1 thymidine kinase (HSV-1-tk) and ganciclovir
► *Escherichia coli* cytosine deaminase and 5-fluorocytosine.

Modifying control genes

In this strategy the gene therapy counteracts a function of the tumour cell that is necessary for tumour growth and spread. Anti-angiogenic factors and tissue inhibitors of matrix metalloproteinases, important in the development, transformation, and invasiveness of HGG, have been evaluated in the laboratory and in pre-clinical studies.

Tumour suppressor genes

This method attempts to restore the function of normal genes, in circumstances where a prior mutation has rendered them ineffective; as part of the carcinogenic process. These genes have been called "tumour suppressor genes" even though they have very important physiological functions. The classic examples are mutations to p53, which acts both as a cell cycle checkpoint switch and a trigger for apoptosis.

Antisense strategies

Antisense mechanisms interfere with the various steps of RNA processing, a major component of gene expression, including transcription, anabolism, and catabolism of mRNA and translation. Achieving tumour specificity without interfering with normal cell function remains a problem. Interference with DNA expression is also a possibility, though the additional problem of intranuclear delivery makes this less attractive.

Immunotherapy (cellular and molecular)

Immunotherapy encompasses a wide variety of treatment avenues aimed at recruiting the immune system and its components in either direct or indirect attack upon the tumour.

► Vaccination with tumour cells (whole or gene modified tumour cells)
► Vaccination against tumour associated antigens (for example, dendritic cell vaccines)
► Lymphocyte therapy (allogeneic or autologous lymphocytes with interleukin-2)
► Monoclonal antibodies have been used both to stimulate immune response, for their direct anti-tumour effect, and to target therapeutic agents, such as toxins and radioisotopes.

Oncolytic viral therapy (or virotherapy)

The majority of viruses currently used in gene therapy trials are replication incompetent. One of their major limitations is the requirement that the virus be delivered to the majority of the tumour cells if it is to be effective. Each viral particle can at best only transfect one tumour cell. In reality, transfection rates are nearer 10% than 100%. Even with the "bystander effect" (the killing of non-transfected cells), there is still a considerable shortfall from what is needed for effective tumour killing. The use of replication competent viruses has the potential to circumvent this problem. A successful infection of a cell and the consequent viral replication results not only in the destruction of the infected cell (viral oncolysis) but also in the release of viral progeny to infect other cells in the vicinity. This can initiate a chain reaction, which under the right conditions, could potentially spread

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throughout the tumour. The mainstay of successful cancer virotherapy is the manipulation of the viral genome to allow replication within tumour but not normal cells. This can be achieved by the insertion of tumour specific promoters or gene inactivation to produce conditional replication. The herpes simplex virus mutant HSV1716 has been the first in human trials in brain tumours.

Biological toxins

A number of protein toxins have been evaluated in vitro and now in clinical studies for their anti-tumour activity, including diphtheria toxin, pseudomonas exotoxin, and ricin. These have been conjugated to a variety of targeting molecules, either specific to or over-expressed by tumour cells, such as monoclonal antibodies, and interleukins 4 and 13. These have entered clinical trial, particularly using CED for delivery, with reasonable promise.

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