Neurological side-effects caused by recently approved chemotherapy drugs

Many recently approved anti-cancer drugs have neurotoxic side-effects, which in some cases limit the dose levels patients can receive. Oncology teams need to know how to check for warning signs and symptoms and how to manage these toxicities to ensure patients receive the optimal therapeutic treatment while minimising severe or chronic side-effects.

Oncologists know only too well that neurotoxicity represents the dose-limiting toxicity for many of the chemotherapy drugs that we have used for decades. This includes drugs such as the vinca alkaloids, cisplatin and paclitaxel, among others. Neurotoxicity is also important with some of our newer chemotherapy drugs, including drugs that are based on older drugs, such as new formulations of paclitaxel (nab-paclitaxel), nucleoside analogues; new alkylating agents such as temozolomide, and new classes of drugs, including proteasome inhibitors and tyrosine kinase inhibitors.

Focusing on cancer drugs approved since 1999, the classes of drug we will discuss include:

- microtubule inhibitors
- DNA-damaging drugs, such as alkylators and platinating drugs
- nucleoside analogues
- proteasome inhibitors
- immunomodulatory drugs (IMiDs)
- angiogenesis inhibitors.

European School of Oncology
e-grandround

ESO presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts, from controversial areas and the latest scientific developments to challenging clinical cases. One of these is selected for publication in each issue of *Cancer World*.

In this issue, David Schiff, co-director of the Neuro-Oncology Center, University of Virginia Health System, Charlottesville, USA, reviews the neurological side-effects associated with some of the more recently approved chemotherapy drugs. The material is based on a review co-authored by Patrick Wen and Martin van den Bent (*Nature Rev Clin Oncology* 6:596–603). Andreas Hottinger, from Geneva University Hospital, Switzerland, hosted a Q&A session during the e-grandround live presentation. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

NEW MICROTUBULE INHIBITORS

Microtubule inhibitors that have been approved in the last 10 years include nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and ixabepilone.

The well-known peripheral neurotoxicity related to paclitaxel is a sensory neuropathy, which tends to be distal and length-dependent in terms of symptomatology. It is thought to be related to microtubule inhibition of axonal transport, which explains why the longest peripheral nerves – to the feet and hand – tend to be affected first.

Paclitaxel itself is a hydrophobic agent and has to be solubilised in a castor oil or Cremophor (polyethoxylated castor oil) vehicle. Because of the risk of allergic reaction, this requires patients to be premedicated with corticosteroids and antihistamines, and administration requires special intravenous tubing. It has long been thought that the Cremophor vehicle itself may be neurotoxic and it has been hypothesised to exacerbate paclitaxel neuropathy.

Nab-paclitaxel

Albumin-bound paclitaxel takes advantage of the fact that albumin is a natural carrier of hydrophobic molecules. This formulation has paclitaxel in the core, surrounded by albumin on the outside. Albumin binds to its natural receptor, the gp60 receptor, and gp60-caveolin binding delivers the drug in transcytotic vesicles across the endothelium to the tumour.

Nanoparticle albumin-bound paclitaxel has a favourable toxicity profile and patients don't require premedication with corticosteroids. The drug can be administered rapidly, which is convenient for patients and centres providing their treatment. The drug has activity in some patients who have breast cancer that is refractory to standard taxanes. As such, the drug has been approved in the United States for metastatic breast cancer.

Initial studies suggested that nanoparticle albumin-bound paclitaxel might have less neurotoxicity than paclitaxel. Unfortunately, subsequent studies have not confirmed this. The neuropathy seen with nanoparticle albumin-bound paclitaxel is a purely sensory neuropathy, which, as with standard paclitaxel, increases in frequency with a higher per cycle dose as well as with weekly administration. At standard doses, about 70% of patients have grade 1, very mild peripheral neuropathy, and up to 10% of patients have grade 3 peripheral neuropathy (based on the NCI Common Toxicity Criteria [CTC] scale), which means neurotoxicity that interferes with activity of daily living. Fortunately, peripheral neuropathy tends to improve fairly rapidly by one to two grades over a median of three weeks when the drug is stopped. Most patients can then be restarted on this formulation with a modest dose reduction.

Ixabepilone

Ixabepilone has a distinct structure from paclitaxel, although it has a ring structure that is somewhat similar. It was the first drug in a new class – the epothilones – and is a macrolide antibiotic derived from a myxobacterium. It binds tubulin, in a similar way to all the taxanes, either at, or very near, to the taxane-binding site.

Like the taxanes, ixabepilone enhances microtubule stabilisation or polymerisation. In a similar way to standard paclitaxel, it is formulated in a Cremophor vehicle. It is active in some patients with taxane-resistant tumours. Unlike paclitaxel, it is not a substrate for P-glycoprotein.

As with taxanes, the chief toxicities with ixabepilone are neuropathies and neutropenia. The neuropathy is very similar to that with paclitaxel. At a standard dose of 40 mg/m^2 every three weeks, about 60% of patients have mild grade 1 peripheral neuropathy and 10%–15% of patients have grade 3 peripheral neuropathy. As with taxanes, patients complain of hand and foot paraesthesias, but motor or autonomic involvement is rare.

Neurotoxicity is cumulative, but tends to improve within a month or two after the drug is discontinued or the dose reduced. We have recommended dose modifications for patients with neurotoxicity (see table below). Baseline neuropathy does not appear to be a contraindication for administration of ixabepilone.

DNA-DAMAGING AGENTS

Oxaliplatin

Oxaliplatin is a platinum drug in the same family as cisplatin and carboplatin. It derives its name from the oxalate moiety attached to its ring structure. Unlike the other approved platinum drugs, this forms bulky DNA adducts. Unlike cisplatin, oxaliplatin does not cause ototoxicity (damage to the auditory nerve), but it has some rare neurotoxicities at high cumulative doses, including blurred vision, ptosis (drooping of the upper eyelid), Lhermitte's sign (an electrical sensation that runs down the back and into the limbs),

DOSE REDUCTION FOR NEUROPATHY WITH IXABEPILONE

Grade 2 ≥ 7 days:	reduce dose by 20% to 32 mg/m^2
Grade 3 < 7 days:	reduce dose by 20% to 32 mg/m^2
Grade 3 ≥ 7 days:	discontinue

urinary retention and reversible posterior leukoencephalopathy syndrome (RPLS, which can cause headaches, confusion, seizures and visual loss). Its main neurotoxicity, which is also its dose-limiting toxicity, is peripheral neuropathy. Peripheral neuropathy with oxaliplatin occurs in both chronic and acute forms.

The chronic neurotoxicity or peripheral neuropathy with oxaliplatin is very reminiscent of the peripheral neuropathy that occurs with cisplatin. It is generally a purely sensory syndrome that tends to manifest as distal sensory loss and paraesthesias. Electrophysiological studies of patients show that this is an axonal neuropathy, or perhaps a neuronopathy or ganglionopathy, because oxaliplatin accumulates in the dorsal root ganglia, which does not have the same blood–nerve barrier as the rest of the peripheral nerve.

The incidence and severity of oxaliplatin neurotoxicity is clearly a function of cumulative dose. Patients treated at a dose of around 800 mg/m^2 have a 15% risk of grade 3 peripheral neuropathy. At a higher cumulative dose, approaching 1200 mg/m^2, fifty per cent of patients treated with oxaliplatin have grade 3 peripheral neuropathy. Unfortunately, this often occurs while the patient is still responding clinically to oxaliplatin.

Another problem that we see both with oxaliplatin and cisplatin is 'coasting', in which patients may worsen clinically or even develop neuropathy for the first time a month or two after discontinuing drug treatment. Most patients make at least a partial recovery from oxaliplatin neurotoxicity, but this tends to be slow, taking months (a median of three months) rather than weeks as with taxanes, and recovery is invariably incomplete as much as six to eight months after treatment is complete.

Acute oxaliplatin toxicity

Acute oxaliplatin toxicity is almost ubiquitous and a unique phenomenon. It consists of cold, exacerbated paraesthesias, which typically involve the hands, feet and perioral regions. Patients can also have these paraesthesias or dysaesthesias in the throat, pharynx or larynx. This can be unpleasant and frightening for patients, giving them the feeling that they're having difficulty breathing or swallowing. However, it is not a true anaphylactic reaction. Patients may become hoarse as result of acute toxicity of oxaliplatin. The onset is generally rapid, within hours of infusion of oxaliplatin, and may last a few days.

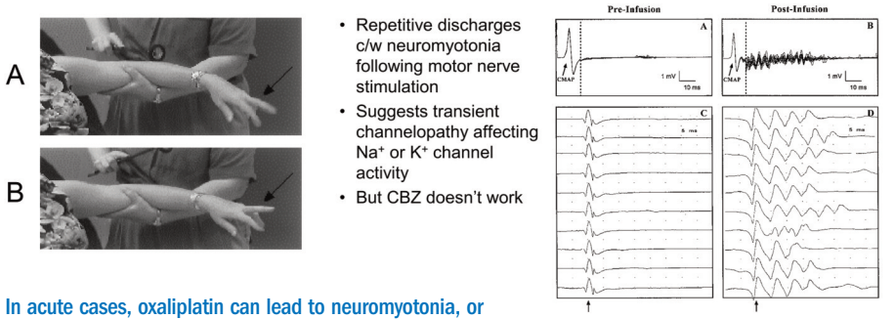
Neuromyotonia is a unique manifestation of acute oxaliplatin neurotoxicity, which results in delayed relaxation. Tapping on the motor branches of the radial nerve – on the posterior interosseous nerve in the forearm – will normally cause a brief contraction lasting up to a few hundred milliseconds. In most patients receiving oxaliplatin there is a sustained contraction lasting several seconds (see figure below).

Repetitive after-discharges are the electrophysiological hallmark of neuromyotonia (see figure). This suggests, as in other causes of myotonia, a transient channelopathy affecting either the sodium or potassium channel. However, carbamazepine, the usual treatment for other causes of neuromyotonia, appears to be ineffective in most patients with oxaliplatin-induced neuromyotonia.

Oxaliplatin peripheral neuropathy – both acute and chronic – represents a clinical problem. The acute neurotoxicity can be managed to some extent by educating patients, so that they're not unduly surprised when they develop symptoms, and they must also be educated to avoid cold exposure. There are some data to indicate that prolonging the infusion of oxaliplatin to decrease the peak dose decreases the risk or intensity of this phenomenon. However, this is not particularly convenient for patients or for infusion centres.

Based on the hypothesis that the oxalate breakdown product of oxaliplatin might chelate calcium and magnesium cations, French investigators did a retrospective cohort study looking at groups pre-treated with calcium and magnesium salts. Results showed that the administration of salts substantially reduced the acute neurotoxicity

DELAYED RELAXATION WITH OXALIPLATIN



In acute cases, oxaliplatin can lead to neuromyotonia, or delayed relaxation, which does not respond to carbamazepine

Source: R Wilson et al. (2002) Acute oxaliplatin-induced peripheral nerve hyperexcitability. *JCO* 20:1767–1774. Reprinted with permission. © 2008 ASCO. All rights reserved

and also decreased the chronic peripheral neuropathy seen with oxaliplatin administration (*Clin Cancer Res* 10:4055–4061).

Based on this observation, two prospective randomised phase III trials were initiated to try to prove this. The first was the CONcePT trial in metastatic colorectal carcinoma. The second was conducted by the Mayo Clinic and the North Central Cancer Treatment Group, using oxaliplatin in the adjuvant setting. Both of these studies randomised patients to calcium and magnesium infusions versus no infusions.

The CONcePT trial was closed early on interim analysis because of a suggestion that tumour response rates were lower in the patients receiving salt infusions. As a result, the North Central trial was closed preliminarily as well. Central review of cases in the CONcePT trial showed that salt infusion did not decrease responsiveness of colorectal carcinoma to oxaliplatin, but, unfortunately, these trials were not reopened.

Data on the effectiveness of salt infusions – in terms of reduction in neuropathy – suggested some benefit. In the CONcePT trial, there was a suggestion of improved patient-recorded outcomes for acute symptoms (*JCO* 26:4010). The North Central trial suggested a decrease in severity and prolonged time to development for chronic peripheral neuropathy (*JCO* 27:15s suppl; abstr 4025). I think it's fair to say the jury is still out, but at the moment it is reasonable to administer these salts prophylactically and there is no evidence that they decrease the effectiveness of oxaliplatin in terms of its chemotherapeutic effect.

Temozolomide

Temozolomide is the neuro-oncologist's favourite drug! It is an oral methylating agent, structurally related to dacarbazine. It achieves very good blood–brain barrier penetration, making it useful in gliomas. Its principal cytotoxic effect seems to be a methylation of the O6 position of guanine in DNA. This O6 methylation is a lesion that is repaired by the DNA repair protein methyl guanine methyl transferase (MGMT).

When temozolomide is administered as a single agent, there is no clearly defined neurotoxicity. However, there is some neurotoxicity when it is combined with radiation therapy for newly diagnosed glioblastoma. The clinical benefit of temozolomide seems chiefly to be in patients who are deficient in MGMT, which fits with our understanding of how it works.

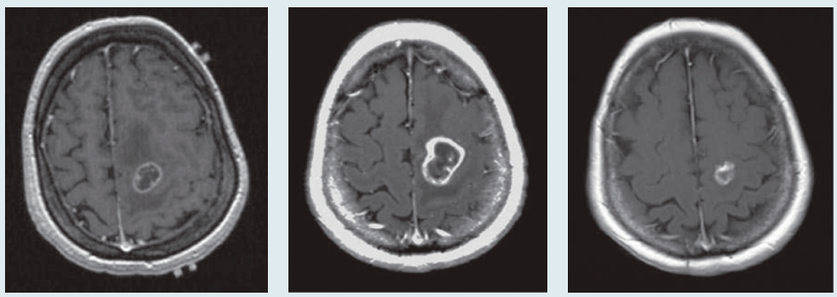
Pseudoprogression

The clinical syndrome of pseudoprogression has been well recognised for decades. Patients treated with radiation therapy for high-grade gliomas sometimes show apparent worsening on a CAT scan or MRI, with an increase in contrast enhancement and increased vasogenic oedema, usually developing several weeks after the completion of fractionated radiotherapy. This is typically a transient phenomenon.

With radiation therapy alone, the literature suggests that pseudoprogession occurs in about 10% of patients treated with usual doses of radiation (up to 60 Gy) for high-grade glioma. Since we've been using temozolomide combined with radiation, we've seen it more frequently, in perhaps 20%–30% of patients.

Looking for a biomarker for pseudoprogression, Brandes and colleagues conducted a study in which just over 100 patients newly diagnosed with glioblastoma were treated with radiation and temozolomide. They were scanned at the conclusion of radiation therapy and half (50) showed a worse-looking MRI scan, while 53 patients had a stable or improved tumour.

A case of pseudoprogression with temozolomide



Pre-RT/TMZ | 1 month post treatment | 1 year post diagnosis

This series of MR scans comes from a woman in her sixties who had a left posterior frontal glioblastoma. The first scan is before radiation therapy. She was then treated with standard radiation and temozolomide. One month after her radiotherapy, her lesion had essentially doubled in diameter, with more vasogenic oedema. We were hopeful that this represented pseudoprogression, so we sat tight and continued her temozolomide. Subsequent scans improved and her one-year scan showed considerable improvement. She is now three years from completion of radiation and remains without evidence of recurrent tumour. In hindsight, this was clearly a case of pseudoprogression.

Regardless of how their MRI looked, the patients were continued on temozolomide and rescanned three months later. About two-thirds of patients whose scans immediately after treatment looked worse, but looked stable or better by this time, were deemed to have had pseudoprogression. Those whose scans looked worse after treatment, and continued to show no improvement, were considered to be resistant to temozolomide treatment and have progressive disease.

Looking at the MGMT status of the patients' tumours (based on promoter methylation) the majority of those with pseudoprogression had MGMT promoter methylation. In the patients who had temozolomide resistance and true tumour progression shortly after completing radiation therapy, the overwhelming majority had unmethylated MGMT promoter analysis (*JCO* 26: 2192–2197). If confirmed in further studies, the MGMT promoter methylation status will help us decide whether a patient is likely to have pseudoprogression or true tumour progression shortly following the conclusion of radiation therapy.

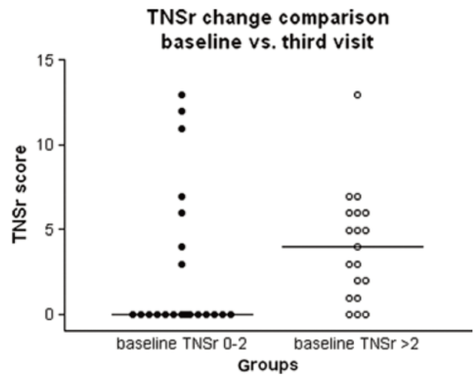
NUCLEOSIDE ANALOGUES

Nucleoside analogues are mostly used to treat haematologic malignancies. Nelarabine is a recently approved Ara-G prodrug that is used to treat patients with T-cell haematologic malignancies. It achieves very good penetration of the blood–brain barrier and has activity in leptomeningeal T-cell malignancies.

Neurotoxicity is very common with nelarabine, affecting around 40% of patients, with about half suffering severe neurotoxicity (of the order of grade 3). This neurotoxicity comes in two different forms: sensorimotor peripheral neuropathy and headache, encephalopathy and seizures.

Clofarabine is a deoxyadenosine analogue that does not cross the blood–brain barrier very well, and is only occasionally associated with mild headache. Cytarabine has been used intrathecally for many years, but a liposomal formulation has been approved more recently. The liposomal formulation almost invariably causes arachnoiditis, manifesting as headache, meningismus and aseptic meningitis-type symptoms. As a result, patients are routinely given prophylactic treatment with dexamethasone (4 mg twice daily). Despite this, mild arachnoiditis-type symptoms are very common. One report, from the group at MD Anderson, suggests that liposomal cytarabine may synergise with either high-dose intravenous methotrexate or cytarabine and predispose patients to neurotoxicity in the form of encephalopathy or corda equina syndrome. This observation requires confirmation.

PERIPHERAL NEUROPATHY AFTER BORTEZOMIB



Painful neuropathy in the hands and feet is a dose-limiting side-effect of bortezomib; the graph shows that it is much more common in patients who had a total neuropathy–reduced (TNSr) score of more than 2 before treatment

Source: F Lanzani et al. (2009) Role of a pre-existing neuropathy on the course of bortezomib-induced peripheral neurotoxicity. *J Peripheral Nerv Syst* 13:267–274 Reprinted with permission. John Wiley and Sons

PROTEASOME INHIBITORS

Bortezomib

Bortezomib is the first proteasome inhibitor approved for use in cancer, and is used to treat multiple myeloma and mantle-cell lymphoma. It is also under study in a number of solid tumour malignancies, including non-small-cell lung cancer and glioblastoma.

Neuropathy represents the dose-limiting toxicity of bortezomib. The mechanism is uncertain but the proteasome is believed to be involved in the degradation of ubiquinated proteins, such as NF-kappaB and cyclins, which help push cells through the cell cycle and are important in haematological cancers. Bortezomib causes peripheral neuropathy by targeting the dorsal root ganglia, where there is no blood–peripheral nerve barrier. Neuropathologically, patients who have had nerve biopsies have shown accumulation of ubiquinated cytoplasmic aggregates.

Bortezomib peripheral neuropathy affects the majority of patients, with 64% having peripheral neuropathy of at least grade 1 severity, but grade 3 neuropathy is relatively uncommon, with a rate of 3%. The neuropathy is almost always purely sensory and tends to affect small fibres. It can be quite painful, with burning paraesthesias and dysaesthesias in the hands and feet. However, neurological examination is usually normal.

Bortezomib neuropathy tends to be cumulative and typically appears around cycle 5, which is about 12 weeks into treatment. It is generally reversible on stopping the drug or reducing the dose. A study

showed that patients with peripheral neuropathy before bortezomib treatment were more likely to develop further neuropathy on treatment than those with lower total neuropathy score (TNS) at baseline (*JPNS* 13:267–274) (see figure, p17).

Immunomodulatory drugs

Thalidomide

Thalidomide is a major agent used to treat both newly diagnosed and recurrent multiple myeloma. It was developed as a sedative about 50 years ago, and its principal acute neurotoxicity is somnolence, which occurs in about 75% of patients. To reduce the problem, thalidomide is given at bedtime, starting with low doses. Tachyphylaxis is common, so most patients habituate to the sedative effect.

However, thalidomide also causes a clinically significant peripheral neuropathy. This tends to have strong sensory and autonomic components, but rarely a motor component. The autonomic component manifests most typically as constipation, which affects the majority of patients. The sensory component appears initially as paraesthesias in the hands and feet. On examining these patients, you will find a distal sensory loss to light touch and pinprick with vibratory sense and deep tendon reflexes somewhat spared.

Thalidomide neuropathy is occasionally painful, although this is not usually a prominent part of the clinical picture. It is an axonal neuropathy. As with the platinum drugs, thalidomide neuropathy can worsen during the first few months after discontinuing the drug and recovery is usually slow and incomplete.

Risk factors for thalidomide neuropathy are debated. Some studies suggest that the daily dose is important, while others argue that it is the cumulative dose. Obviously, cumulative dose is related to daily dose, and it appears that a lifetime cumulative dose greater than 20 g can increase the risk of thalidomide neuropathy. Gabapentin is sometimes helpful, as the paraesthesias are unpleasant for the patient, but there are no drugs that reverse the peripheral neuropathy.

The usual recommendation for thalidomide neuropathy is to discontinue the drug. If the patient's condition is worsening and there is no other alternative, we put thalidomide treatment on hold until the neuropathy has improved and then restart at a much lower dose. As both thalidomide and bortezomib are active against multiple myeloma, this combination is under study. However, reports suggest an increased risk of peripheral neuropathy.

Lenalidomide

Lenalidomide is another immunomodulatory drug approved for the treatment of multiple myeloma and myelodysplastic syndrome. It tends to cause much more myelosuppression than thalidomide, but less central and peripheral neurotoxicity. Neuropathy is rare and mild even at high doses. Fatigue and somnolence are also rare. Occasionally, patients have non-specific symptoms such as dizziness or tremor.

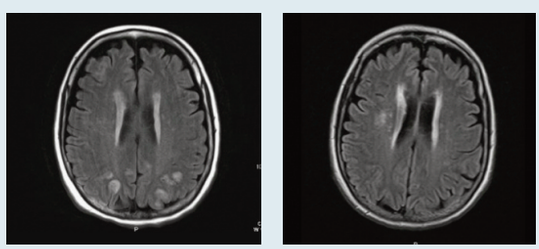
Antiangiogenic agents

Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported with all of the new angiogenesis inhibitors that target vascular endothelial growth factor (VEGF) and its receptor. This syndrome manifests as encephalopathy, seizures, cortical blindness, headache and, generally, very elevated blood pressure. It occurs not only with chemotherapeutic drugs but also with immunosuppressive drugs such as cyclosporine, and in patients with eclampsia and dialysis patients with renal failure.

The pathogenesis remains unclear, but seems to be either a failure of cerebral vasomotor autoregulation or some kind of toxic endothelial injury. This syndrome has been reported both with anti-VEGF agents and VEGF receptor tyrosine kinase inhibitors including sorafenib and sunitinib.

Intracerebral bleeding has been a concern with all anti-angiogenesis inhibitors, including bevacizumab and VEGF tyrosine kinase inhibitors in patients with brain metastases and with bevacizumab in glioblastoma. Use of bevacizumab has long been considered a 'no-no' in patients with brain metastases, since 1997,

A case of reversible posterior leukoencephalopathy syndrome



These MRI scans are of a woman in her sixties with melanoma metastatic to lymph nodes, but not the brain, who was being treated with bevacizumab plus temsirolimus in a clinical trial. She developed a blood pressure of 170/110 mmHg and severe headaches. Her MRI (*left*) showed T2 and FLAIR-hyperintense lesions in the posterior cerebral hemispheres, as well as in the posterior fossa (not shown on the scan). Her hypertension was treated aggressively and bevacizumab was discontinued. A follow-up MRI three weeks later (*right*) showed substantial improvement.

when a patient with hepatocellular carcinoma and an unrecognised brain metastasis in one of the early studies developed an intracranial haemorrhage. This is not withstanding the fact that patients with hepatocellular carcinomas often have coagulopathies and haemorrhagic metastases.

Earlier this year, researchers using Genentech databases published retrospective data looking at the safety of bevacizumab in patients with brain metastases. In the first part of this study, including more than 8000 patients treated with chemotherapy plus or minus bevacizumab, about 100 patients in each of those arms turned out to have brain metastases. Results did not show an elevated rate of intracranial haemorrhage in patients treated with bevacizumab, which is a somewhat reassuring finding.

The study also included more than 4000 patients who had been treated with bevacizumab and then developed brain metastases while on the drug, in open-label, single-arm studies. More than 300 patients developed brain metastases and fewer than 1% of these developed intratumoural haemorrhage (*Clin Cancer Res* 16: 269–278). The researchers concluded that there did not appear to be a disproportionate risk with the use of bevacizumab in the treatment of brain metastases and recommended that we consider not excluding patients with brain metastases from treatment with bevacizumab.

A further prospective study looking at this issue, the PASSPORT study, included more than 100 patients with non-squamous non-small-cell lung cancer and brain metastases. Their brain metastases were resected or irradiated with standard radiation or radiosurgery. They were then treated with whatever standard chemotherapy their oncologist wanted to administer plus bevacizumab.

Patients were followed with brain CT scans or MRI scans at regular intervals, with the endpoint being grade 2 or higher CNS haemorrhage. They were allowed to receive anticoagulants, which were given to almost one-fifth of the patients. No cases of intracranial haemorrhage of any grade were seen, which again supports the idea that bevacizumab can be safely used in patients with treated brain metastases (*JCO* 27:5255–5261).

VEGF RECEPTOR TYROSINE KINASE INHIBITORS

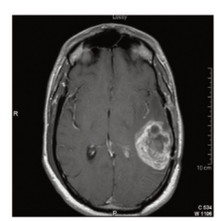
There have been anecdotal reports of intracranial haemorrhage with sunitinib and sorafenib. However, these drugs are widely used for renal cell carcinoma, which is a tumour with a predisposition to haemorrhage – particularly in the brain – even without any specific treatment.

The results of two large, expanded-access open-label studies have been published in the last few months. In the first – a study of more than 300 patients with brain metastases from renal cell carcinoma, who were treated with sunitinib – only one patient had a low-grade intracranial haemorrhage (*Lancet Oncol* 10:757–764). In the second – which included 70 patients with brain metastases from renal cell carcinoma, treated with sorafenib – no intracranial haemorrhages occurred (*Cancer* 116:1272–1280). The authors of both of these reports concluded that the tyrosine kinase inhibitors appeared to be reasonably safe in patients with treated brain metastases.

The oncologic community is well aware that bevacizumab is a useful agent in recurrent glioblastoma. The figure below shows MR scans from a patient with recurrent glioblastoma before and after bevacizumab who was in a trial that led to approval by the FDA. There has long been concern about using bevacizumab for glioblastoma because of the fact that glioblastomas occasionally haemorrhage even without bevacizumab, and the brain is obviously a bad place for an intratumoural haemorrhage.

GLIOBLASTOMA BEFORE AND AFTER BEVACIZUMAB

- GBMs occasionally haemorrhage
  - 1/21 HGG pts receiving bevacizumab had fatal bleed
- Friedman et al. (*JCO* 2009): 167 recurrent GBM
  - 3 gr 1, 1 gr 2, 1 gr 4 haemorrhage
- Kreisl et al. (*JCO* 2009): 0 haemorrhages/48 GBM pts
  - Friedman allowed LMWH, Kreisl didn't
- 21 pts bevacizumab + anticoagulant at UCLA (*Neuro Oncol* 2008)
  - 2 asymptomatic, 1 mildly symptomatic bleeds
  - Risk of bleeding with anticoagulant acceptable



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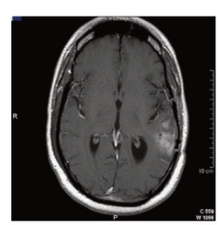

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These scans were part of the pivotal study that led to FDA approval of bevacizumab in recurrent glioblastoma; a number of small studies suggest that the risk of intracranial haemorrhage in this setting is 'acceptable'

GBM – glioblastoma multiforme, HGG – high-grade glioma, LMWH – low molecular weight heparin, *Source:* Scans courtesy of David Schiff

In a small study on the use of bevacizumab in recurrent high-grade glioma, 1 in 21 patients had a fatal intracranial haemorrhage (unpublished). A larger study of 167 patients with recurrent glioblastoma multiforme treated with bevacizumab, and allowed to receive anticoagulants if they had venous thromboembolism, found that only five patients had intracranial haemorrhage, and these were mostly of low grade (*JCO* 27:4733–4740).

Similarly, in the report from Howard Fine's group at the National Cancer Institute, none of the patients treated with bevacizumab developed haemorrhages (*JCO* 27:740–745). As such, it appears that the risk of intratumoural haemorrhage with bevacizumab in recurrent glioblastoma – although still not clearly defined – is acceptably low.

The issue of whether patients who are receiving bevacizumab and are on anticoagulants can be safely treated in view of the risk of haemorrhage was looked into by Tim Cloughesy's group at UCLA. They reported 21 patients who were anticoagulated for venous thromboembolism while receiving bevacizumab. There were two asymptomatic and one mildly symptomatic haemorrhages (*Neuro Oncol* 10:355–360).

Overall, the neurological community has accepted a small risk of bleeding with anticoagulation and bevacizumab.

Q&A

Andreas Hottinger, from Geneva University Hospital, Geneva, Switzerland, hosted a question and answer session with David Schiff.

Q: *What is the maximum dose of oxaliplatin for the treatment of colorectal cancer that patients can tolerate? Is there a limit, and, if so, how do you work with that?*

A: I generally leave this decision to my medical oncology colleagues who are administering the chemotherapy. I think that, in the absence of clinically significant neuropathy, there is no reason not to keep going as long as the patient is tolerating oxaliplatin. Obviously, it is a difficult decision if the patient has mild to moderate neuropathy, but is still responding to the drug. That is a decision for the oncologists to make.

Q: *What kind of work-up do you recommend for patients who develop neuropathy on treatment?*

A: The first thing is to try to characterise the neuropathy clinically and then to determine whether it fits with the chemotherapy that the patient has been receiving. Most chemotherapy neuropathies have a distal predilection and they tend to be symmetric. Most of the neuropathies I discussed are either purely sensory or more sensory than motor. We try to sort out from the patient's history and examination if their neuropathy fits with that. Electrophysiological testing is needed in only a minority of patients. One of the great uses of EMG and nerve conduction studies is to determine if a neuropathy is axonal or demyelinating. Most of the chemotherapy neuropathies are axonal neuropathies. Obviously, excluding other possible causes of peripheral neuropathy like alcohol use or diabetes is important. The main use of electrophysiology is to help sort out whether patients have an underlying hereditary neuropathy or an acquired demyelinating polyneuropathy that either is mimicking the chemotherapy neuropathy or is predisposing to a more severe chemotherapy neuropathy.

Q: *Once the patient has developed a neuropathy, what kind of supportive measures do you recommend?*

A: We do not have any proven neuroprotective agents, with the possible exception of calcium and magnesium salts with oxaliplatin. Therapy tends to be symptomatic. I don't believe vitamins have been proven to be of much use, except for avoiding nutritional deficiencies in cancer patients that can exacerbate peripheral neuropathy. Treatment is therefore symptomatic with agents such as gabapentin, vigabatrin, amitriptyline and sometimes low-dose opioids for painful neuropathy.

Q: *Why do chemotherapy neuropathies tend to affect sensory neurons over motor neurons, and why do motor neurons appear to be protected from their effects?*

A: The speculation is that the motor neurons are located in the spinal cord, which is protected by the blood–spinal cord barrier. The peripheral nerves may be particularly vulnerable through the dorsal root ganglion, which lies outside the protection of the blood–nervous system barrier.

Q: *What do you suggest for the effective diagnosis of pseudoprogression and its treatment?*

A: We have not found any imaging techniques to be reliably useful. As such, we generally continue temozolomide for at least three months following completion of fractionated radiotherapy, unless the patient has developed disease outside the radiation field.