as chemoradiation add to the burden of disease. In a randomised EORTC study in 386 patients with anaplastic oligodendrogliomas, the effect of combined procarbazine, lomustine, and vincristine (PCV) chemotherapy after radiotherapy was compared with radiotherapy. Quality of life was measured using EORTC questionnaires on quality of life and on brain cancer. During and shortly after chemotherapy, there was a major negative effect on quality of life due to nausea and vomiting, loss of appetite, and drowsiness. However, no long-term detrimental effects could be detected in patients receiving both radiotherapy and PCV chemotherapy. Thus, the beneficial effects of adjuvant PCV chemotherapy on prolonging progression-free survival in patients with anaplastic oligodendrogliomas, particularly in the subset of patients with combined loss of heterozygosity on chromosome arms 1p and 19q, are not being offset by durable side-effects. In a study of 363 patients with low-grade or high-grade gliomas, 205 patients had depression, anxiety, or both. Patients with high-grade gliomas had significantly less anxiety than did those with low-grade disease (odds ratio 0·361, 95% CI 0·203–0·641). Multivariate analysis showed that men had a 36% lower risk of depression than did women, and a history of psychiatric problems was associated with an increased risk of current depression.

This study highlights the importance of attention to psychological factors and complements advances in recognition of independent prognostic factors and molecular characteristics of the tumour. Nomograms based on long follow-up data from chemoradiotherapy in glioblastoma multiforme can now help to predict the prognosis of the individual patient.

Charles J Vecht
Neuro-oncology Unit, Department of Neurology, The Hague Medical Center, POP 432, 2501 CK The Hague, Netherlands c.vecht@michaaglanden.nl

I have no conflicts of interest.


For the EORTC nomograms see http://www.eortc.be/tools/ gbmcalculator

Neurological infections: advances in therapy, outcome, and prediction

Important studies on CNS infections published in the past year have highlighted therapeutic advances and improved understanding of prognosis. Furthermore, the application of sophisticated molecular biological techniques has increased our knowledge of disease pathogenesis and helped to facilitate diagnosis.

Case fatality rates from community-acquired bacterial meningitis have changed little over the past quarter of a century. The recognition that host inflammatory and cytokine responses contribute to pathogenesis has led to clinical trials of adjuvant steroid therapy. In 2002, a prospective, randomised, double-blind trial in 301 adult European patients with bacterial meningitis found that treatment with dexamethasone was associated with a decrease in death rates by about 50% (from 15% to 7%; relative risk 0·48) and a decrease in unfavourable outcomes by about 40% (from 25% to 15%; 0·59). Benefit from dexamethasone was significant only in patients with meningitis caused by Streptococcus pneumoniae. Recently, in a randomised, double-blind,
placebo-controlled study of 435 Vietnamese patients, dexamethasone lowered the risk of death at 1 month by 57%, but this benefit was seen only in the subgroup of patients with definite bacterial meningitis. Only patients with infection caused by gram-positive bacteria benefited from treatment with this drug. Dexamethasone non-significantly increased the risk of death in patients with “probable” meningitis, possibly due to inclusion of patients with undiagnosed, and therefore untreated, tuberculous meningitis. Given the lack of benefit of steroid therapy in patients who have meningitis and a coexisting HIV infection, the practical message for clinicians is that steroids should probably be reserved for immunocompetent patients whose cerebrospinal fluid (CSF) gram stain shows a gram-positive organism.

In patients with bacterial meningitis, physicians often struggle to determine the potential effects of prior antibiotic therapy on the CSF. A recent retrospective cohort study, in which 85 children received antibiotic pretreatment, focused on these possible effects. Prior antibiotic therapy considerably decreased the incidence of positive bacterial cultures in the CSF (from 88% to 70%) and blood cultures (from 66% to 48%), but did not decrease the frequency of positive CSF gram stains (from 63% to 62%). The duration (0–24 h) of antibiotic pretreatment was not associated with significant differences in CSF white blood cell or absolute neutrophil counts, but longer therapy was associated with higher CSF glucose and lower protein concentrations. The study indicates that care should be taken when using glucose and protein measurements in the CSF to distinguish between bacterial as opposed to viral meningitis in patients who have received antibiotic pretreatment. However, such pretreatment does not affect CSF white blood count, percentage of lymphocytes and neutrophils, or frequency of positive gram stains.

West Nile virus (WNV) is the most important cause of arboviral neuroinvasive disease in the USA. A recent longitudinal cohort study in 149 Canadian patients used a variety of validated test instruments to assess long-term mental and physical impairment after WNV infection. The estimated time that patients took to achieve 95% of the maximal predicted score for each test was determined. The time to maximal predicted score for patients with neuroinvasive disease was 139 days (95% CI 63–388) for mood, 148 days (69–274) for fatigue, and 455 days (166–1354) for mental function. The only category in which patients with neuroinvasive and non-neuroinvasive disease differed was in recovery of physical function, in which patients with neuroinvasive disease needed 175 days (99–334) compared with only 121 days (98–153) for those with non-neuroinvasive disease. So far, this is the best study to investigate sequelae and recovery times after WNV infection and suggests that, although convalescence can be prolonged, most patients return to normal levels of functioning within 1 year.

Sophisticated molecular biological approaches have been increasingly used to investigate the pathogenesis of viral CNS infections and to help diagnosis. In a recent study, RNA interference was used to screen for human genes associated with WNV susceptibility and resistance. 283 host susceptibility factors and 22 host resistance factors were identified. The screen identified sets of genes that encode proteins that regulate cellular processes, such as nucleic acid metabolism (n=50), signal transduction (n=47), protein metabolism (n=44), cell structure, motility, and adhesion (n=37), ion and biomolecular transport (n=28), and intracellular protein trafficking (n=27). The screen also identified several genes (n=18) that are known to be involved in host immunity, including defensins, immunophilins, and interferon-associated proteins, such as an RNase L inhibitor. All 22 of the WNV host resistance factors also
inhibited infection by dengue (another flavivirus), but only five of the 22 decreased infection by HIV-2, which suggests that there was substantial pathogen specificity in host resistance factors. Silencing of only 36% of the 283 WNV host susceptibility factors decreased dengue infection, which suggests that susceptibility factors might greatly differ even for closely related viruses. Sophisticated studies of this type are likely to identify novel targets for antiviral therapy.

The potential of new high-throughput molecular biological techniques to assist in the identification of unknown causes of infection was highlighted by a recent report of a new lymphocytic choriomeningitis (LCMV)-like virus that causes transplant-associated infections.7 A 57-year-old man served as a liver and kidney donor for three women in Australia; all three organ recipients developed a fatal febrile encephalopathy 4–6 weeks after transplantation. When standard diagnostic techniques failed to identify a pathogen, unbiased high-throughput sequencing was used as a pathogen discovery tool. Potential protein sequences identified were used to search GenBank databases; 14 protein sequence fragments were consistent with arenavirus proteins with a high homology to LCMV. With this information, RT-PCR, with appropriately designed primers, detected arenavirus RNA in tissue, blood, and CSF specimens from the transplant recipients. The sequences amplified had 79–97% homology at the amino acid level with specific LCMV proteins, suggesting that the inciting virus was closely related, but not identical, to LCMV. Furthermore, arenavirus antigen and arenavirus particles were detected in Vero cells inoculated with fresh-frozen kidney from one recipient. This study established the promise of high-throughput sequencing for the diagnosis of CNS infections.

To paraphrase Niels Bohr and Yogi Berra, prediction is always difficult, particularly about the future. DNA sequencing seems to be following a Moore’s Law-like trajectory as sequencing throughput is increasing and the cost of every nucleotide sequenced is falling. Rapid, high-throughput sequencing approaches and related molecular biological tools will soon become routinely used to identify potential pathogens in situations in which standard approaches have failed, will enable us to search for novel candidate pathogens in neurological disease of potential infectious origin, and will let us manipulate cellular pathways for antimicrobial therapy.

Kenneth L Tyler
University of Colorado Denver Health Sciences Center, and Denver Veterans Affairs Medical Center, Denver, CO 80220, USA
ken.tyler@uchsc.edu

I have received expert consulting fees from Macrogenics, Genentech, Biogen Idec, Sanofi Pasteur, and Boehringer Ingelheim.