combination treatment was 175 days, with median survival among the five who died being 190 days and that among the five survivors being 166 days at last analysis. In a recent pilot/pharmacokinetics study, Dr Dieterich and colleagues found that twice daily foscarnet 90 mg/kg IV was associated with pathologic and endoscopic improvement in 90% of patients with CMV GI disease, with full resolution of symptoms occurring in 80% of patients and partial resolution occurring in 10%. Dr Dieterich noted that confirmation of such findings could have a financial impact, since the 90 mg/kg bid regimen can be administered at home, whereas the 60 mg/kg tid regimen must be administered in the hospital; he also related that the former regimen has been reported to be effective in treatment of CMV retinitis in European experience.

The role of maintenance therapy for CMV GI disease after initial treatment remains unclear. In a study scheduled to begin soon, patients with upper or lower CMV GI disease will receive foscarnet 90 mg/kg IV bid for 4 weeks followed by randomization to maintenance treatment or no maintenance treatment. In an ACTG study that is currently under way, a pharmacokinetic analysis of oral ganciclovir maintenance treatment is to be performed in patients with CMV colitis after 3 weeks of ganciclovir-induction therapy. ■

Developments in CMV Disease Treatment

Developments in CMV disease treatment were discussed at the Boston meeting by W. Lawrence Drew, MD, PhD, from the Mt Zion Medical Center of the University of California at San Francisco.

Diagnostics

As related by Dr Drew, advances in CMV diagnostics include wide availability of a novel CMV antigenemia assay, involving staining of peripheral blood samples with tagged monoclonal antibodies, that permits documentation of CMV viremia on a same-day basis. According to Dr Drew the antigen assay is also an effective means of documenting CMV central nervous system (CNS) disease. Although initial experience with the test in Dr Drew's laboratory suggested 60% to 70% accuracy compared with blood culture, continued use in their hands and at other laboratories has shown sensitivity approaching 90% to 100%. Dr Drew stated that the shell vial assay, which can provide results within 24 hours, has proven to also have high accuracy in detecting viremia according to blood culture standards. A particular virtue of the antigen assay is the ability to quantitate viremia. For example, it is possible that a correlation between degree of viral antigenemia and CMV wasting syndrome will be demonstrated. Another diagnostic development, the branched-DNA assay for measuring levels of CMV DNA in the blood, also provides quantitative results. Dr Drew presented an example in which a patient developed CMV retinitis 3 weeks after persistent increased viral DNA levels were initially detected on the assay, followed by levels falling below detection limits at 10 days after initiation of ganciclovir treatment. As related by Dr Drew, the branched-DNA assay may thus prove to be of value in predicting onset of disease, as well as providing a practical method for monitoring patients during treatment—eg, for documenting an antiviral effect and then its dimunition in association with resistance. Similar considerations apply to quantitative PCR techniques that are currently undergoing adaptation for routine clinical use.

Resistance

Studies performed by Dr Drew and colleagues several years ago indicate that CMV isolates resistant to ganciclovir can be isolated in approximately 10% of patients after 3 months of treatment. The majority of cases of resistance are due to mutation in the viral kinase required for initial phosphorylation of ganciclovir. Rare cases are attributable to mutation in cellular DNA polymerase, and double mutations may occasionally occur. As noted by Dr Drew, resistance is manifest by progressive increases in drug 50% effective doses (ED-50s) over time and appears to be the result of selection of preexisting mutants in the viral population. The viral kinase mutations that have been associated with resistance include substitutions at amino acid residues 460 and 595 in the UL97 or protein kinase gene. As stated by Dr Drew, given successful adaptation for routine clinical laboratory use, use of PCR to detect such mutations in clinical isolates may prove valuable in patient management, providing extremely rapid identification or prediction of resistance compared with current culture-based phenotypic assays. He noted that resistant genotypes are identified by PCR only when they constitute at least approximately 10% of the viral population in an individual sample and that this threshold level appears to correlate with initial increases in ED-50s. Thus, it is unlikely that detection of resistant genotypes by PCR would significantly antedate development of phenotypic resistance.

Development of resistance to foscarnet was expected to occur less frequently than ganciclovir resistance, given that foscarnet does not require phosphorylation to its active form. Studies at Dr Drew's laboratory have indicated that whereas all ganciclovir-sensitive CMV strains remain susceptible to foscarnet, approximately half of ganciclovir-resistant strains also exhibit reduced sensitivity to foscarnet. Dr Drew suggested that these isolates may exhibit DNA polymerase resistance mutations or double mutations. According to data from a Studies of the Ocular Complications of AIDS (SOCA) patient group presented by Dr Drew, there was an equivalent increase in the proportion of both ganciclovir-treated and foscarnet-treated patients becoming blood culture-positive over time on treatment after initial conversion to negative culture. This suggests a similar rate of resistance development in patients receiving the two drugs, but definitive interpretation will follow the results of antiviral resistance testing of all isolates. According to Dr Drew, information on the incidence of resistance in SOCA patient isolates and on the relationship of resistance to clinical events in these patients may be available before year end.

Oral ganciclovir

As related by Dr Drew, study of the effects of oral (1 to 3 g/d) and IV (5 mg/kg/d) ganciclovir on CMV titer in semen of infected patients over 28 days has shown that both forms of ganciclovir are associated with decreased titers in the majority of patients. Although the antiviral effect of the oral form is reduced compared with the IV drug, in association with poor bioavailability, the need for an oral agent for use in prophylaxis and maintenance and the documentation of meaningful antiviral activity by the oral agent have prompted performance of a number of trials of oral treatment. According to Dr Drew, preliminary data from a large-scale preventive study are expected by year end and enrollment of a community consortium prevention trial is nearly complete. Maintenance trials include one in which patients were randomized to oral or IV maintenance after IV induction therapy and one in which patients already on IV maintenance were offered the choice of continuing on IV or switching to oral maintenance. Data from

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more than 100 patients in the former maintenance study were presented by Dr Drew. Progression determined by funduscopic examination was found to be significantly delayed by IV ganciclovir at the standard maintenance dosages compared with oral ganciclovir at a dosage of 3 g/d, with the mean times to progression in the groups being 96 days and 68 days, respectively. However, there was no significant difference between IV and oral groups with regard to progression according to masked reading by ophthalmologists of retinal photographs taken at the time of funduscopic examination, with mean times to photographic progression being 62 days in the IV group and 57 days in the oral group. In addition, there was no difference between the two groups with regard to deterioration of visual acuity at any time point. There was no significant difference between proportions of IV and oral patients found to be culture positive during maintenance treatment. Dr Drew noted that oral ganciclovir can be given in dosages up to 6 g/d and that a trial examining this higher dosage in maintenance treatment is under way. No increased incidence of GI adverse effects was observed in oral patients, with the only notable difference in adverse events being a greater incidence of IV line sepsis and fever in the IV group.

HPMPC

The investigational anti-CMV agent HPMPC is a nucleotide analogue with the structure of a monophosphorylated drug, allowing the agent to bypass the step of phosphorylation via viral kinase. Cellular phosphorylation converts the agent to its active diphosphate form. In theory, HPMPC, like foscarnet, may be of greater prophylactic utility than ganciclovir, since it should be present in active form in CMV-uninfected cells. Similarly, like foscarnet, it may pose greater risk of overall cellular toxicity than ganciclovir, since its activity is not selective for infected cells. In an initial dose-escalating study, Dr Drew and colleagues have found both that the agent has significant nephrotoxic potential and that nephrotoxicity can be reduced by modification of the regimen. A modified regimen consisting of concomitant probenecid administration, hydration, dosing interval extension, and interruption for proteinuria appeared to be beneficial in this regard. As noted by Dr Drew, a feature of treatment with HPMPC of potentially great impact is that the agent can be given as induction therapy on a once-weekly basis and as maintenance therapy on a biweekly basis by 1 hour infusion; suppression of viral replication over between-dose intervals of up to 3 weeks has been observed.

CMV CNS infection

According to Dr Drew, polyradiculopathy in association with CMV infection is becoming an increasingly common problem, with presentation characterized by lower extremity pain and weakness and bladder incontinence. CSF abnormalities uncommon to viral infections, including polymorphonuclear pleocytosis, with an average WBC count of 400/μL, and moderately low glucose levels, are observed in patients with the condition in the absence of any other potential etiologic agent. Dr Drew stated that CMV culture of the CSF may be negative in one third to one half of cases, whereas branched-DNA and CMV antigen assays appear to provide accurate diagnosis. Data presented by Dr Drew showed that both of these assays proved positive in each of nine cases of polyradiculopathy while culture was positive in only six. There are data indicating that patients with CMV polyradiculopathy who are not treated have an average survival of 3 weeks, with none showing stabilization or improvement, and that treated patients have an average survival of 11 weeks, with approximately half showing stabilization or improvement. Dr Drew presented data showing progressive decreases in CSF CMV levels on branched-DNA testing in six of seven polyradiculopathy patients during treatment with ganciclovir and/or foscarnet. He suggested that the relatively poor outcome in treated patients is thus not due to absence of antiviral effect, but rather to the irreversible nature of CNS damage; it is thus imperative to make the diagnosis of CSF infection in a timely manner. He also noted the potential utility of techniques such as the CMV antigen and branched-DNA assays in rapidly indicating absence of antiviral effect in CSF, presenting data from one polyradiculopathy patient in whom CMV titers continued to increase during ganciclovir treatment, presumably in association with resistance to the agent.

Other treatment developments

Dr Drew related a number of other recent findings or developments in the area of treating CMV disease. Results of a small comparative study in CMV retinitis patients reported by Jacobson and colleagues indicate that foscarnet maintenance therapy with 120 mg/kg may be superior to the commonly used 90 mg/kg regimen; the higher dosage increased time to progression from 31 to 95 days and survival time from 5.1 months to 11.0 months compared with the lower dosage. In a study reported at the 1993 International Conference on AIDS in Berlin of approximately 50 patients with upper or lower GI CMV disease, Blanshard et al found foscarnet and ganciclovir to be comparable in effectiveness, producing similar rates of endoscopic improvement (81% vs 84%), histologic improvement (81% vs 95%), and symptomatic response (90% vs 90%), with adverse effects occurring in 31% of foscarnet patients and 24% of ganciclovir patients. More foscarnet patients had other GI pathogens (35% vs 12%). In a study by Tolpin et al, also reported at the 1993 International Conference on AIDS, biweekly IV administration of CMV monoclonal antibodies in combination with ganciclovir or foscarnet treatment in patients with CMV retinitis was associated with a median time to remission of >200 days. Prospective trials involving such combination treatment are planned. Dr Drew noted that another promising agent in early stages of development is cyclobut-G. This agent, which is similar to ganciclovir and is structurally described as deoxyguanosine with sugar replaced by a cyclobutyl ring, exhibits 40% oral bioavailability, a level greatly exceeding the bioavailability of oral ganciclovir.

Finally, Dr Drew described a sustained-release device that is capable of delivering drug into the vitreous of the eye for nearly 6 months. The device, which is sutured in place, is currently being evaluated in a trial in which CMV retinitis patients are receiving intravitreal ganciclovir alone or in combination with IV or oral drug. Dr Drew noted that despite the characteristic systemic nature of CMV disease, some retinitis patients who have received only intravitreal drug have responded remarkably well; he suggested that the device may have utility in patients without significant systemic disease or those incapable of tolerating systemic treatment. ■