Treatment of cytomegalovirus retinitis: A growing number of options

In 1980, one year before the recognition of AIDS, there were approximately 30 cases of cytomegalovirus (CMV) retinitis (CMVR) documented in the world literature (1). Now in 1996, many clinicians have seen more than 30 cases of CMVR apiece. Early in the AIDS epidemic, CMVR was recognized as a major opportunistic infection in AIDS patients (2). Subsequent observations have indicated that CMVR eventually develops in approximately 25% of human immunodeficiency virus (HIV) -infected individuals (3), usually occurring in advanced HIV disease when CD4 lymphocyte count is less than 50×10^6/L (4).

CMVR usually presents as painless visual loss. In four series containing over 100 cases each, there was bilateral involvement at initial presentation in 34% to 42% of patients (3-7). In the absence on antiviral therapy, the majority of patients who present with unilateral disease go on to develop bilateral disease (3), and blindness in one or both eyes can result. Hence, effective therapies are clearly needed. The current therapies and options for their administration follow.

INTRAVENOUS GANCICLOVIR

Initial effects to treat CMVR with intravenous ganciclovir began in 1984 (8). Uncontrolled reports of clinical efficacy were supported by retrospective case-control studies (9) and confirmed by a prospective, randomized study comparing immediate ganciclovir therapy with deferred treatment in patients with nonsight-threatening, peripheral CMVR (10). This study demonstrated a median time to progression of 13.5 days with deferred therapy compared with 49.5 days with immediate treatment. Subsequently, it was observed that CMVR would reappear rapidly upon cessation of ganciclovir therapy. A randomized, clinical trial published in 1988 demonstrated the need for maintenance therapy because the median time to progression of CMVR was 16 days in the absence of maintenance therapy compared with 42 days with maintenance therapy (11).

FOSCARNET

Despite the efficacy of ganciclovir, alternative therapies are necessary because of the high relapse rate associated with ganciclovir therapy as well as the hematopoietic suppressive effect, which make it more difficult to use other myelosuppressive drugs in these patients. Foscarnet was the agent next studied for CMVR, and in a pilot study of 14 patients conducted in Toronto (12), seven experienced a complete response and seven had a partial response to therapy. Subsequently, a controlled trial verified the efficacy of foscarnet in CMVR (13).

Foscarnet and ganciclovir have been directly compared as initial therapy for CMVR (5,14), and the two agents were of equivalent efficacy in the treatment of CMVR, but toxicity necessitated a switch from foscarnet to ganciclovir more often than the reverse. The principal toxicities of foscarnet are nephrotoxicity and electrolyte imbalance. Foscarnet is also associated with the development of seizures and requires a considerable amount of intravenous fluid (approximately 3 L/day) for its administration. It is widely perceived that intravenous foscarnet is associated with a greater adverse effect on quality of life than intravenous ganciclovir. On the other hand, a study comparing foscarnet with ganciclovir demonstrated that patients randomized to foscarnet had improved overall survival (relative risk 1.79; 95% CI 1.17 to 2.73). Part of the explanation for this survival difference was that patients assigned to the ganciclovir group received less antiretroviral therapy than those assigned to the foscarnet group; however, this did not adequately explain the excess mortality. Despite the possible survival advantage of foscarnet therapy, intravenous ganciclovir remains the preferred initial therapy because of its more favourable adverse event profile and its easier administration. In addition to intravenous ganciclovir and foscarnet, several new therapies are available for the treatment of CMVR. Unfortunately, there are no current data assessing the comparative efficacy of most of these therapies with either intravenous ganciclovir or foscarnet.

CIDOFOVIR

The third parenteral option is cidofovir. Cidofovir is a nucleotide analogue active against CMV that requires infrequent dosing because of the prolonged intracellular half-life of its bioactive metabolites (15). Induction therapy consists of two weekly infusions following by maintenance therapy every two weeks. Efficacy has been confirmed in a prospective, randomized trial comparing immediate treatment with delayed treatment in a subset of patients with peripheral nonsight-threatening CMVR (16). The median time to progression was 22 days with delayed therapy and 120 days with immediate therapy. Cidofovir can be nephrotoxic, but this can be minimized by preloading with intravenous saline and administering probenecid 3 h before infusion as well as 2 h and 8 h after completion of the 1 h infusion.

ORAL GANCICLOVIR

Another new systemic therapy, which is used only for maintenance treatment, is oral ganciclovir. Oral ganciclovir in a dose of 1 g three times daily is as efficacious as intravenous ganciclovir at a dosage of 5 mg/kg body weight once daily for the maintenance phase of CMVR treatment in a group of patients who initially received three weeks of intravenous ganciclovir induction therapy and in whom evidence of initial stabilization of retinitis was demonstrated on two consecutive ophthalmologic examinations (6). Oral ganciclovir has not been evaluated as induction therapy and should not be used for maintenance therapy until the effectiveness of induction therapy has been confirmed by an ophthalmologist. A major concern regarding oral ganciclovir has been its poor oral bioavailability of 2.6% to 7.3% (17). A newer, more bioavailable formulation of oral ganciclovir is under development.

INTRAVITREAL GANCICLOVIR

In addition to systemic therapy for CMVR local, intraocular therapy has been also studied. The greatest experience is with ganciclovir. Ganciclovir may be administered by intermittent intravitreal injection or by a sustained-release ganciclovir intraocular implant. Initially, intravitreal ganciclovir was used in patients in whom the toxicity of intravenous ganciclovir was so severe that it could not be used. In initial, uncontrolled studies, favourable results were seen in most treated eyes (18,19). The long term outcome of this strategy has been confirmed (20). The advantages of intravitreal therapy are the ability to deliver higher concentrations of drug to the site of disease and the avoidance of systemic drug toxicity. The disadvantages include the need for the patient to present to an ophthalmologist for treatment, the limited number of practitioners skilled to administer this therapy, the risk of bacterial endophthalmitis and retinal detachment from the injection, and the lack of systemic prophylaxis against CMV elsewhere in the body, including the contralateral eye for those patients with unilateral disease.

To obviate the need for repeat intraocular injections and repeat visits to an ophthalmologist, a sustained-release ganciclovir intraocular implant has been designed and evaluated. In a randomized clinical trial the ganciclovir implant was highly effective, with a median time to progression of disease of 226 days compared with 15 days in a deferred therapy control group of patients with peripheral, nonsight-threatening retinitis (21). In another randomized clinical trial, the implant was directly compared with itravenous ganciclovir (22), and a significantly longer median time to CMVR progression was achieved with the implant (202 days versus 88; $P<0.001$). Although this device obviates the need for repeat intraocular injections, it requires implantation by a retinal surgeon under general anesthesia and carries risks of bacterial infection and retinal detachment. The implant costs approximately $5,000; most clinicians feel that patients will require systemic prophylaxis to prevent disease in the contralteral eye and other organs, usually with oral ganciclovir. In addition, the rate of ganciclovir release by the device is variable, and the reservoir requires exchange at approximately 32 weeks.

INTRAVITREAL FOSCARNET AND CIDOFOVIR

Finally, there have been pilot studies of intraocular therapy with foscarnet injections (23) and cidofovir injections (24). The data regarding these two intraocular therapies are extremely limited, and definitive recommendations cannot be made at this time.

EXPERIMENTAL THERAPIES

ISIS 2922, also known as fomivirsen, is a phosphorothioate oligonucleotide designed to be complementary to mRNA encoding the major immediate-early proteins of CMV (25). ISIS 2922 is active against CMV in vitro and has been developed for intravireal use. Intravitreal ISIS 2922 has been used predominantly as a salvage therapy for refractory CMVR, but is now being studied as an alternate primary therapy. High doses of intravitreal ISIS 2922 have been associated with decreased peripheral vision and retinal pigment epithelial stippling, but these adverse effects may be acceptable when used as salvage therapy. Lower doses of this agent are being studied for primary therapy.

A human monoclonal antibody to CMV, known as MSL 109, which is given intravenously, has been studied as an adjunctive therapy in CMVR. In a recent randomized trial of 209 patients, the median time to progression was unaffected by adjunctive MSL 109 therapy, but there was excessive mortality in the group of MSL 109-treated individuals, which was seen only in the 60% of study subjects who were treated for relapsed CMVR and not in those undergoing initial induction therapy (26).

WHICH THERAPY TO USE?

Despite the availability of several effective therapies, the only direct comparisons of therapies for initial induction therapy have been that between intravenous ganciclovir and foscarnet, as noted above (5,14), and between intravenous implants (22). The implants is an excellent choice for sight-threatening disease, but is seldom an option in Canada due to lack of reimbursement. In practice, the choice of therapy is guided by criteria such as patient preference, physician preference, tolerance for side effects, funding considerations (particularly third-party drug and/or device reimbursement) and the expertise and opinions of local retinal specialists. Once a successful induction therapy has been found, there are limited data comparing maintenance regimens. As noted above, there has been a direct comparison of intravenous versus oral ganciclovir, and the two therapies are equivalent after initial successful intravenous ganciclovir induction therapy. However, the nearly inevitable progression of the disease on current maintenance regimens suggests that more effective maintenance regimens need to be developed, or perhaps the current practice of reducing the doses of anti-CMV therapy during the maintenance phase needs to be re-evaluated.

The management of progressive disease on antiviral therapy has been the subject of a randomized, comparative trial (27). In this study, patients were randomized to reinduction with the same agent they received previously (either ganciclovir or foscarnet), induction with the opposite drug or induc-

tion with both ganciclovir and foscarnet. Combination therapy was the most effective regimen for controlling retinitis, but combination therapy was poorly tolerated and was associated with the greatest adverse impact on quality of life measures. Even when successful reinduction is achieved, the time to next progression is progressively shorter with each successful induction (6). Thus, while combined ganciclovir and foscarnet therapy is more effective than either drug alone for retreatment, this combination of drugs is not well tolerated, particularly considering the many other drugs that HIV-infected patients with extremely low CD4 lymphocyte counts are often receiving.

CONCLUSIONS

Since the recognition of CMVR as a major opportunistic infection in AIDS patients in the early 1980s, therapeutic options have evolved from no therapy to intravenous ganciclovir to a choice among ganciclovir, foscarnet, cidofovir or intraocular ganciclovir administered by repeat injection or sustained-release intraocular implant. The availability of multiple options provides choice for patients and physicians, particularly when there are contraindications to one or more therapies. Regrettably, there are inadequate comparative data regarding the relative efficacies of these therapies, for both induction and maintenance. Direct comparisons of the available therapies for initial therapy, maintenance therapy and retreatment are urgent priorities.

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