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Zalcitabine

An Update of Its Pharmacodynamic and Pharmacokinetic Properties and Clinical Efficacy in the Management of HIV Infection

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Contents

Summary

Synopsis

Zalcitabine is a dideoxynucleoside antiretroviral agent that is phosphorylated to the active metabolite 2',3'-dideoxycytidine 5'-triphosphate (ddCTP) within both uninfected and HIV-infected cells. At therapeutic concentrations, ddCTP inhibits HIV replication by inhibiting the enzyme reverse transcriptase and terminating elongation of the proviral DNA chain.

The results of 3 large pivotal trials comparing zidovudine monotherapy with combination therapy have now clearly established that zalcitabine plus zidovudine combination therapy improves survival, delays disease progression and is associated with an improvement in viral load and CD4+ cell count compared with zidovudine monotherapy. More recently, clinical end-point and surrogate marker data have established the efficacy of zalcitabine in combination with the protease inhibitor saquinavir in zidovudine-experienced patients. Other studies have demonstrated the utility of zalcitabine in combination with ritonavir and the nucleoside analogue lamivudine. Importantly, early use of zalcitabine in the treatment sequence does not appear to limit the therapeutic efficacy of subsequent therapy with other nucleoside analogues such as lamivudine.

Peripheral neuropathy is the most frequent dose-limiting adverse effect associated with zalcitabine therapy and is generally reversible on discontinuation of treatment. Stomatitis and mouth ulcers may occur frequently with zalcitabine therapy but tend to resolve with continuing treatment. Haematological toxicity, which is a common adverse effect associated with zidovudine, is reported infrequently with zalcitabine. Overall, combination therapy with zalcitabine plus zidovudine or saquinavir has been shown to have a tolerability profile comparable to that of either agent alone, although treatment with zidovudine plus zalcitabine was associated with a significant increase in the incidence of haematological toxicity compared with zidovudine monotherapy in one study.

Therefore, current data suggest that zalcitabine is a useful antiretroviral agent for inclusion as a component of initial double combination therapy with zidovudine or as part of triple combination therapy including zidovudine plus a protease inhibitor in the management of patients with HIV infection.

Pharmacodynamic Properties

Zalcitabine is phosphorylated to the active antiviral compound 2',3'-dideoxycytidine 5'-triphosphate (ddCTP) within both uninfected and HIV-infected cells. ddCTP inhibits HIV replication by inhibition of the enzyme reverse transcriptase and termination of viral DNA chain elongation. In both these roles ddCTP competes with endogenous deoxycytidine triphosphate. Zalcitabine has demonstrated significant antiretroviral activity against HIV-1 *in vitro*. In addition, synergistic antiretroviral activity has been reported for zalcitabine in combination with several other antiretroviral agents including zidovudine, stavudine and saquinavir.

Resistance to zalcitabine usually arises from a series of mutations within the HIV *pol* gene and develops less frequently than resistance to zidovudine. Cross-resistance between zidovudine and zalcitabine has been described. The activation state of the target cell, whether the cell under investigation is acutely or chronically infected with HIV, and/or the levels of intracellular phosphorylating enzymes may also contribute to variation in the antiviral activity of zalcitabine between cell lines.

In vitro investigations suggest that zalcitabine-induced inhibition of an enzyme responsible for the synthesis of mitochondrial DNA (DNA polymerase γ)

may be responsible for the development of peripheral neuropathy in clinical practice.

Pharmacokinetic Properties

Following oral administration, zalcitabine is rapidly absorbed, with peak plasma concentrations typically achieved in 1 to 2 hours. The oral bioavailability of zalcitabine exceeded 80% in some studies. Zalcitabine partially crosses the blood-brain barrier; drug concentrations in the CSF represented a mean of 14 to 20% of simultaneously measured plasma concentrations. Placental transfer of zalcitabine has been reported *in vitro* and *in vivo*.

Zalcitabine has a short plasma elimination half-life of 1.1 to 1.8 hours and is predominantly excreted unchanged in the urine. Hepatic metabolism of the drug is minimal and only about 10% of an orally administered dose is excreted in the faeces.

Clinical Efficacy

The results of 3 large pivotal studies, ACTG 175, CPCRA 007 and Delta, have clearly demonstrated that combination therapy with zidovudine plus zalcitabine or zidovudine plus didanosine improves survival and delays disease progression compared with zidovudine monotherapy. Although not exclusively limited to zidovudine-naive patients, the benefits of zalcitabine plus zidovudine therapy appear to be greater in this patient population than in zidovudine-experienced patients. Improvements in surrogate marker and clinical end-points have also been reported in zidovudine-experienced patient populations with advanced HIV infection (CD4+ cell count 50 to 300 cells/μl) treated with 2- or 3-drug combination regimens comprising zalcitabine plus the protease inhibitor saquinavir ± zidovudine. Zalcitabine has also demonstrated utility in combination with the protease inhibitor ritonavir as first-line treatment in a pilot study. Impressive surrogate marker data have also been reported in zidovudine-experienced patients receiving a 3-drug regimen comprising lamivudine, zalcitabine and zidovudine. Furthermore, the addition of lamivudine ± loviride to ongoing therapy with zidovudine plus zalcitabine in patients with advanced HIV infection was associated with a greater reduction in disease progression compared with the addition of lamivudine ± loviride to zidovudine alone. This therefore suggests that prior use of zalcitabine does not limit the subsequent utility of other nucleoside analogues such as lamivudine.

Tolerability

Peripheral neuropathy is the major dose-limiting adverse effect associated with zalcitabine therapy and has been reported to occur in 12 to 46% of patients in clinical studies; risk factors for the development of zalcitabine-induced peripheral neuropathy include a baseline CD4+ count ≤50 cells/μl, diabetes mellitus and a low serum cobalamin level. Mouth ulcers and stomatitis occurred with an incidence of 3 to 4% in 3 large studies and 29% in a fourth study; these effects may resolve with continuing administration of the drug. Pancreatitis is an infrequent adverse effect associated with zalcitabine therapy, generally developing in <1% of patients. Other adverse effects associated with zalcitabine include hepatotoxicity and cutaneous/hypersensitivity reactions.

The tolerability profile of combination therapy with zalcitabine plus zidovudine or saquinavir generally reflects that of the individual drugs and has not been associated with the development of any unexpected adverse effects. However, the incidence of haematological adverse effects with zidovudine plus zalcitabine therapy was significantly greater than that reported for zidovudine alone in one study.

Although tolerability data in children are limited, rash, stomatitis and peripheral neuropathy have been reported after administration of the drug to this patient group.

Drug Interactions

Several important drug interactions have been reported between zalcitabine and other drugs used in the management of patients with HIV infection. Potentially nephrotoxic agents, notably the aminoglycosides, amphotericin and foscarnet, may reduce the renal clearance of zalcitabine and potentially increase the incidence of zalcitabine-associated adverse effects. Importantly, the concomitant use of zalcitabine with pentamidine should be avoided because of an increased risk of the development of severe pancreatitis. Furthermore, zalcitabine should be coadministered with caution with other drugs that may cause peripheral neuropathy (for example, didanosine, dapsone, metronidazole, stavudine, isoniazid and pentamidine) should be avoided where possible. A reduction in the bioavailability of zalcitabine has been reported with the concomitant administration of aluminium hydroxide/magnesium hydroxide antacid mixture.

To date, clinically significant pharmacokinetic interactions have not been reported between zalcitabine and other antiretroviral agents including zidovudine, saquinavir and nevirapine. However, inhibition of zalcitabine phosphorylation by lamivudine has been reported *in vitro*.

Dosage and Administration

The recommended dosage of zalcitabine for use in combination with zidovudine in adults and adolescents (age >13 years) is 0.75mg administered orally every 8 hours. The same dosage is recommended for use in combination with the protease inhibitor saquinavir. The optimal dosage of zalcitabine as part of triple combination therapy has yet to be determined, although 0.75mg every 8 hours has been widely used in clinical studies.

Zalcitabine dosage should be reduced in patients with renal insufficiency; 0.75mg twice daily is recommended in patients with a creatinine clearance (CL_{CR}) of 0.6 to 2.4 L/h (10 to 40 ml/min) decreasing to 0.75mg once daily in patients with a CL_{CR} <0.6 L/h (<10 ml/min). Zalcitabine should be discontinued if peripheral neuropathy develops and reinstituted (at a dose of 0.375mg every 8 hours) only if symptoms become no more than mild in nature. Caution is also recommended when the drug is administered to patients with a history of poor bone marrow reserve, elevated amylase levels, pancreatitis or alcohol abuse and in patients receiving parenteral nutrition.

Zalcitabine (2′,3′-dideoxycytidine, ddC) is a dideoxynucleoside that is active against HIV. Since the publication of the original review of zalcitabine in *Drugs* in 1992[1] there has been a considerable increase in published data on the use of this drug, particularly in combination with other antiretroviral agents, in the treatment of HIV infection. This review updates the original zalcitabine review and incorporates data published during the past 5 years.

1. Overview of Pharmacodynamic Properties

1.1 Mechanism of Action

Following cellular uptake, zalcitabine is phosphorylated to the active metabolite 2′,3′-dideoxycytidine 5′-triphosphate (ddCTP) by intracellular phosphorylating enzymes in both uninfected and HIV-infected cells.[2] Zalcitabine competes with

natural cellular deoxycytidine for these enzymes. The triphosphate metabolite of zalcitabine then competes with endogenous deoxycytidine triphosphate (dCTP) for the enzyme HIV reverse transcriptase; inhibition of this enzyme subsequently prevents viral DNA synthesis and HIV replication. Viral DNA synthesis is also terminated through incorporation of ddCTP in place of dCTP into the growing retroviral DNA chain, preventing addition of subsequent nucleosides (see review by Whittington & Brogden[1]).

1.2 *In Vitro* Antiviral Activity

Analysis of the *in vitro* activity of antiviral agents is dependent upon a large number of variables including cell type, activity of intracellular phosphorylating enzymes, levels of endogenous dCTP pools and stage of infection (see section 1.4.2).[3] Because of potential modulation of antiviral activity by cytokines and competition between endogenous dCTP and ddCTP for reverse transcriptase active sites, variations in the *in vitro* activity of zalcitabine in different cell lines have been reported. Furthermore, the use of a variety of assay conditions makes between-study comparisons difficult.

Zalcitabine 0.5 μmol/L showed significant antiviral activity against HIV-1 in human T cell lines with almost complete inhibition of cytopathic effects and p24 antigen expression.[4] However, current single agent antiretroviral drug regimens are insufficient to provide long term viral suppression in patients with HIV infection because of the development of drug-resistant viral strains. For this reason, interest is now focused on the use of combinations of antiretroviral agents which additively or synergistically inhibit HIV replication (see section 3.2) and may delay or prevent the emergence of viral resistance. Although *in vitro* synergy does not automatically correlate with clinical benefit, it nevertheless has an important role in the selection of suitable antiretroviral agents for use in combination in the clinical setting.[3]

Numerous studies have evaluated the *in vitro* activity of zalcitabine in combination with other agents, most notably zidovudine. The results of studies evaluating 2- and 3-drug combinations are summarised in table I.

Table I. *In vitro* activity of zalcitabine in combination with other agents against laboratory HIV-1 strains

Reference	Drug[a] (class)	Cell culture[b]	Result
Double combination			
Brennan et al.[5]c	MKC-442 (NNRTI)	C8166, MT4, JM	+
Bridges et al.[6]	FTC (NRTI)	MT2	+
Chong et al.[7]c	Delavirdine (NNRTI)	PBM, H9	++
Connell et al.[8]	Saquinavir (PI)	CEM	++
Craig et al.[9]	Zidovudine (NRTI)	CEM, MT4	++
	Saquinavir (PI)	CEM, MT4	++
Craig et al.[10]	Saquinavir (PI)	CEM-T4	++
Degré & Beck[11]	Human leucocyte interferon (I)	PBM	++
Deminie et al.[12]	Stavudine (NRTI)	CEM-SS	++
Eron et al.[13]c	Zidovudine (NRTI)	H9, PBM	++
Johnson et al.[14]d	Saquinavir (PI)	PBM	+/++
Mathez et al.[15]d	Zidovudine (NRTI)	PBM	++
Palmer et al.[16]c	Foscarnet (NNRTI)	PBM	++
Perno et al.[17]	GM-CSF (CSF)	M/M-enriched PBM	–
Perno et al.[17]	M-CSF (CSF)	M/M-enriched PBM	–
Taylor et al.[18]	MDL-28574 (α-GI)	H9, MT4	++
Triple combination			
Craig et al.[9]	Saquinavir (PI) plus zidovudine (NRTI)	CEM, MT4	++

a Drug used in combination with zalcitabine.

b All studies used cell viability (usually dye exclusion) and/or p24 antigen production to measure anti-HIV activity except Craig et al.[10] (HIV syncytium formation). C8166, CEM-SS, CEM, CEM-T4, H9, JM, MT2 and MT4 are T cell lines.

c Both laboratory strains and clinical HIV-1 isolates tested.

d Only clinical HIV-1 isolates tested.

Abbreviations and symbols: α-GI = α-glucosidase 1 inhibitor; CSF = colony-stimulating factor; FTC = 2,3′-dideoxy-5-fluoro-3′-thiacytidine; GM-CSF = granulocyte-macrophage colony-stimulating factor; I = immunomodulator; M-CSF = macrophage colony-stimulating factor; M/M = monocyte-macrophage; PBM = peripheral blood mononuclear cells; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; – indicates antagonistic effect; + indicates additive effect; ++ indicates synergy.

Progressively greater inhibition of viral replication (denoted by a delay in breakthrough of HIV-1 replication) was reported with an increasing number of drugs in a CD4+ T cell line (H9); 4-drug

therapy (zidovudine, didanosine, interferon and zalcitabine) was more effective than triple therapy (zidovudine, didanosine and interferon), which in turn was more effective than zidovudine plus didanosine.[19]

As intracellular phosphorylation is necessary for the antiretroviral activity of zalcitabine, investigations have focused on whether the concomitant administration of other drugs may modify this process and potentially reduce the *in vitro* antiviral activity of zalcitabine. Using peripheral blood mononuclear cells (PBMs), and U937 and MOLT 4 cell lines, zidovudine, didanosine and stavudine were shown to have no significant effect on zalcitabine phosphorylation.[20] Similarly, zalcitabine did not significantly reduce the intracellular phosphorylation of zidovudine in PBM or the h1A2v2 lymphoblastoid cell line.[21] In contrast, the nucleoside analogue lamivudine inhibited zalcitabine phosphorylation *in vitro*.[22] The clinical relevance of this interaction is currently unknown; however, both lamivudine and zalcitabine are dependent upon deoxycytidine kinase for the initial steps of phosphorylation. The anthracycline anticancer agent doxorubicin also inhibited zalcitabine phosphorylation *in vitro*.[20] Conflicting results have been reported regarding the effect of ribavirin, a broad spectrum antiviral agent, on the phosphorylation and antiviral activity of zalcitabine.[20,23]

1.3 Cytotoxicity

Zalcitabine is toxic to erythroid and granulocyte-macrophage progenitors, predominantly in the early stages of differentiation.[24] *In vitro*, zalcitabine inhibited bone marrow cell development at concentrations that showed minimal antiviral activity. This suggested that zalcitabine may be associated with haematotoxicity similar to that of zidovudine[25,26] but this has not been unequivocally confirmed in clinical trials (see section 4). Potentially important myelotoxicity developed in the HL60 myeloid leukaemia cell line following prolonged exposure to combination therapy with zidovudine and zalcitabine, with or without didanosine.[27] However, brief periods of exposure (4 hours) to triple drug combinations had only a modest myelotoxic effect.

In MOLT-4, CEM, PC 12 and U937 cells, treatment with zalcitabine reduced mitochondrial DNA content, impaired mitochondrial function and/or produced mitochondrial ultrastructural changes.[28-32] Defective replication of mitochondrial DNA is thought to be responsible for the development of peripheral neuropathy in patients treated with nucleoside analogues such as zalcitabine.[33-35] Indeed, abnormal Schwann cell mitochondria, with decreased myelin mitochondrial RNA and axonal neuropathy, were reported *in vivo* in rabbits treated with zalcitabine.[36]

Preliminary data suggest that zalcitabine may be associated with less embryonic cytotoxicity than zidovudine. Cytotoxicity in murine 2-cell embryos was significantly lower with zalcitabine than zidovudine; inhibition of blastocyst formation was evident at zidovudine 1 μmol/L but only became detectable at zalcitabine 100 μmol/L.[37]

In US National Toxicology Program studies, a poorly regenerative macrocytic anaemia, which was reversible on cessation of treatment, was reported in mice given zidovudine and to a lesser extent in mice that received zalcitabine.[38] Furthermore, in contrast to didanosine, zalcitabine did not alter murine immune function through modification of the antibody response. Other workers investigated the *in vivo* toxicity of zalcitabine using the LP-BM5 murine retrovirus-induced immunodeficiency model.[39] Histological examination revealed a marked reduction in the number of megakaryocytes in the bone marrow of both infected and uninfected mice and hepatocellular vacuolation in the liver of uninfected mice only. In addition, a reduction in mitochondrial DNA content was reported in both groups.

1.4 Resistance to Zalcitabine

1.4.1 Viral Resistance

The development of viral resistance to antiretroviral drugs is a major cause of treatment failure. *In vivo* resistance to zalcitabine or any other

anti-HIV agent is a consequence of the extremely high replication rate of the wild-type virus and to a lesser extent to the high rate of incorporation of errors by HIV reverse transcriptase.[40-43] This results in the continuous and spontaneous generation of viral mutants, including drug-resistant mutants, even in the absence of drug. Replication of these mutants usually occurs at a low rate; however, when the wild-type virus is suppressed by drug therapy, one or more drug resistant mutants, which are already present at low levels, can replicate freely and predominate. The development of viral resistance to nucleoside analogues has been reviewed by several authors.[41-45]

Several mutation sites in the HIV *pol* gene have been associated with resistance to zalcitabine,[46] although data from clinical studies suggest that HIV develops reduced susceptibility to zalcitabine less frequently than to zidovudine.[47-50] Current data suggest that the level of resistance to zalcitabine is generally equivalent to a <100-fold increase in IC_{50} (concentration of drug required to inhibit viral replication by 50%). Mutations at codons 65 or 69 are typically associated with only modest resistance to zalcitabine (<10-fold reduction in IC_{50}).[41] The mutation at codon 69 is the most frequently observed change in viral isolates from patients developing resistance to zalcitabine[48,51] but importantly does not appear to lead to cross-resistance to didanosine or zidovudine.[41,43] Mutation at codon 65 has been associated with resistance to zalcitabine, didanosine and lamivudine[52,53] and it may cause a reduction in viral DNA chain termination in the presence of ddCTP[54] and selective changes in the ability of reverse transcriptase to recognise ddCTP.[55] A low level of *in vitro* resistance to zalcitabine and didanosine (4- to 8-fold increase in IC_{50}) and a marked increase in *in vitro* resistance to lamivudine (500- to 1000-fold) have been associated with a mutation at codon 184.[56,57]

Therapy with zidovudine and zalcitabine during alternate months has been associated with the selection of clinical isolates resistant to both drugs.[47,58] However, in 3 studies (Delta, ACTG 106 and BW 34,225-02), treatment of zidovudine-naive patients (<4 weeks of prior zidovudine therapy) with zidovudine plus zalcitabine for 48 or 112 weeks resulted in the selection of predominantly zidovudine-resistant strains.[50,59,60] In 2 of these studies, the use of combination therapy was not associated with an appreciable delay in the emergence of zidovudine-resistant viral isolates.[50,60] In a subgroup analysis of zidovudine-naive patients recruited to the Delta study, the development of zidovudine resistance caused by a mutation at codon 70 was significantly ($p < 0.0001$) delayed during combination therapy (zidovudine plus zalcitabine or didanosine) compared with zidovudine monotherapy; however, there was no significant difference between the treatment groups in time to the development of other resistant mutations associated with zidovudine.[59] Notably, the pattern of resistance to zalcitabine both as monotherapy and as combination therapy has led to suggestions that the use of this drug early in the treatment sequence does not limit future therapy options.[41,43]

Mutations conferring cross-resistance to zalcitabine have been reported. A mutation at codon 75 conferring cross-resistance to stavudine, zalcitabine and didanosine has been described *in vitro*.[61] Workers have also reported a novel mutation pattern (at codons 62, 75, 77, 116 and 151) in patients receiving zidovudine plus zalcitabine or didanosine which confers cross-resistance to stavudine.[62] A virus with mutations at positions 75, 77, 103, 116, 151 and 184 which is resistant to all nucleoside analogues and most non-nucleoside reverse transcriptase inhibitors tested has also been described recently in a heavily pretreated patient.[63] Notably, resistance to zalcitabine, stavudine and nevirapine has been reported in clinical isolates obtained from patients who had been previously treated with zidovudine only.[64]

1.4.2 Cellular Resistance

In addition to the selection of drug-resistant variants of HIV, the selection of drug-resistant cell populations may play an important role in reducing the antiretroviral activity of nucleoside analogues.[65,66] Currently available data suggest that

individual nucleoside analogues differ in their activity against various target cell lines and have shown zalcitabine to be more effective in monocyte-macrophage than in T cell lines.[67] A reduction in intracellular levels of dCTP, which competes with ddCTP for reverse transcriptase, is thought to contribute towards the greater activity of zalcitabine in monocyte-macrophage cell lines.[68,69] Differences in the level of intracellular phosphorylating enzymes may also contribute to variations in the anti-HIV activity of zalcitabine among cell lines.[70] Notably, levels of deoxycytidine kinase are exceedingly low in brain tissue, suggesting that zalcitabine is not extensively metabolised in the brain.[71]

Other factors associated with cellular drug resistance include the activation state of the target cell and whether the cell under investigation is acutely or chronically infected with HIV. In contrast to zidovudine, which preferentially protects activated cells from HIV infection, the antiviral effect of zalcitabine was reported to be greater in resting cells.[72-74] In common with zidovudine and didanosine, zalcitabine has antiviral activity at subtoxic concentrations in *de novo* infected monocyte-macrophages but lacks antiviral activity at concentrations 1000 times greater in chronically infected cells.[75]

Selection of a zalcitabine-resistant U937 monoblastoid cell line characterised by an increased number of mitochondria, greater mitochondrial DNA content and a reduction in the affinity of cytoplasmic deoxycytidine kinase for zalcitabine has been reported following long term exposure to the drug.[31,76,77]

2. Pharmacokinetic Properties

The pharmacokinetic properties of zalcitabine have been investigated after oral and intravenous administration to adults and children with HIV infection (table II) and have been reviewed previously by several authors.[1,82-85] Pharmacokinetic data on the administration of zalcitabine to pregnant or elderly patients or to patients with hepatic impairment are currently unavailable. Pharmacokinetic data from children are limited, but suggest lower bioavailability and/or faster clearance of zalcitabine in children compared with adults (table II).[80,81]

Table II. Mean pharmacokinetic data for zalcitabine. Results after single dose administration of zalcitabine in adults and children with HIV infection

Reference	Zalcitabine dose (mg) [no. of pts]	C_{max} (μg/L)	AUC (mg/L • h)	F (%)	V_{ss} (L/kg)	$t_{1/2\beta}$ (h)	CL
Adults with AIDS or ARC							
Gustavson et al.[78]	0.5 PO [2]	7.6	0.018	86		1.5	
	0.5 PO[a] [1]	8.5	0.019			1.1	
	5 PO [4]	79.0	0.208	100		1.8	
	0.5 IV [4]	10.5	0.022		0.64	1.3	0.336 L/h/kg
Klecker et al.[79]	0.09-0.5/kg PO [7]	95-316[b]		88			
	0.03-0.25/kg IV [10]	84-158[c]			0.54	1.2	13.62 L/h/m^2
Children with symptomatic HIV infection							
Gould Chadwick et al.[80]	0.02/kg PO[a] [23]	9.3	0.025			1.4	0.876 L/h/kg
Pizzo et al.[81]	0.03-0.04/kg PO [5]	40	0.061	54	9.3 L/m^2	0.91	
	0.03-0.04/kg IV [5]	76	0.135			0.78	8.94 L/h/m^2

a Oral solution.

b Range of values for 4 patients who received zalcitabine 0.25 mg/kg PO.

c Range of values for 4 patients who received zalcitabine 0.09 mg/kg IV.

Abbreviations: ARC = AIDS-related complex; AUC = area under the plasma concentration-time curve; CL = total body clearance; C_{max} = peak plasma concentration; F = oral bioavailability; IV = intravenous; PO = oral; pts = patients; $t_{1/2\beta}$ = terminal plasma elimination half-life; V_{ss} = volume of distribution at steady-state.

Extensive evaluation of the disposition of zalcitabine was initially hampered by the limitations of analytical methods available to measure the low plasma concentrations achieved after the administration of clinically relevant doses.[78] However, the recent development of radioimmunoassay methods for the measurement of plasma zalcitabine concentrations has overcome this problem.[86-88]

2.1 Absorption and Distribution

Zalcitabine has a linear pharmacokinetic profile which is not significantly affected by the route of administration (oral or intravenous).[78] After oral administration of zalcitabine 0.25 mg/kg to adults, the drug was rapidly absorbed, with peak plasma concentrations of 95 to 316 μg/L typically achieved in 1 to 2 hours.[79] After oral administration of tablets or solution to adults, the bioavailability of zalcitabine has been reported to exceed 80%.[78,79] Concomitant administration of zalcitabine with food reduced zalcitabine bioavailability by 14% and decreased the mean plasma concentration by 39%; however, these changes were not considered to be of clinical importance.[89]

The concentration of zalcitabine in the CSF after oral or intravenous administration was 14 to 20% of that simultaneously measured in the plasma of patients with AIDS or AIDS-related complex (ARC).[79,90]

2.2 Metabolism and Elimination

Zalcitabine is rapidly eliminated, with a plasma elimination half-life ($t_{½\beta}$) of 1.1 to 1.8 hours and a total body clearance of approximately 14 L/h/m^2 (233 ml/min/m^2) reported in adults (table II). Urinary excretion of unchanged drug is the principal route of elimination of zalcitabine, accounting for 62% and 75% of single oral and intravenous doses, respectively.[79] Following a single oral dose of zalcitabine (0.75mg), clearance of the drug was reported to be significantly ($p < 0.05$) reduced in patients with a creatinine clearance (CL_{CR}) ≤3 L/h (≤50 ml/min) [n = 15] compared with those with a CL_{CR} >3 L/h (>50 ml/min) [n = 8], suggesting the need for dosage adjustment in patients with poor renal function (see section 6).[91]

Zalcitabine does not appear to undergo significant hepatic metabolism; dideoxyuridine (ddU) is the primary metabolite of zalcitabine found in the urine. Approximately 10% of an orally administered dose of zalcitabine is excreted in the faeces, primarily as unchanged drug or ddU.[92]

3. Clinical Efficacy

Because of the slowly progressive course of HIV infection, the use of primary clinical endpoints (survival, disease progression and development of an AIDS-defining event) to assess the efficacy of antiretroviral therapy in clinical trials may not be feasible, particularly in patients who are asymptomatic at recruitment. The scale of the HIV epidemic warrants rapid evaluation of drug efficacy and tolerability and has led to the introduction of surrogate markers of disease as an indirect assessment of drug efficacy.

Plasma viral load and rate of CD4+ cell depletion are currently considered to be the best predictors of disease progression/death.[93] CD4+ cell count, however, has been shown to be a poor on-therapy marker of response in efficacy studies of antiretroviral drugs.[94,95] Instead, plasma viral load is now emerging as a more accurate predictor of disease progression and clinical outcome for patients receiving antiretroviral therapy;[96,97] the results of study ACTG 175 showed a significant association between plasma HIV RNA levels and risk of disease progression and death in patients treated with zidovudine, zalcitabine and/or didanosine.[98] Other less frequently used surrogate markers include p24 antigen, β_2-microglobulin and serum neopterin levels.[93] While the use of surrogate markers is widely accepted, their value remains a controversial issue.[99,100]

The majority of studies evaluating zalcitabine in the treatment of HIV infection have used both clinical and surrogate markers. Such studies have recruited both asymptomatic and symptomatic zidovudine-experienced and zidovudine-naive patients. Since the previous review of zalcitabine in

Drugs,[1] the clinical profile of this agent has been more extensively delineated, most notably in large randomised double-blind studies comparing oral zalcitabine (2.25 mg/day) as a component of combination therapy with zidovudine monotherapy in HIV-infected adults; only a small number of studies have been conducted in children (section 3.3) and no further studies in this patient population are planned. The value of combination antiretroviral therapy over monotherapy in the treatment of patients with HIV infection has now been unequivocally demonstrated in several large phase III studies. In clinical practice this has resulted in the widespread substitution of antiretroviral combination therapy for monotherapy as standard treatment in patients with HIV infection. For this reason, studies evaluating the use of zalcitabine in combination with other antiretroviral agents are the focus of the clinical section of this review and only brief reference is given to monotherapy studies.

Whether zalcitabine is an effective antiretroviral agent for the prevention of HIV transmission during the perinatal period,[101-103] following occupational HIV exposure[104,105] or in the management of patients with AIDS dementia complex[106-109] has yet to be determined.

3.1 Zalcitabine Monotherapy

In view of the recent widespread adoption of combination antiretroviral therapy as standard care for patients with HIV infection, the use of zalcitabine monotherapy in clinical practice is no longer appropriate. Prior to this change in practice, several comparative studies were conducted comparing zalcitabine with zidovudine or didanosine monotherapy. The largest of these (ACTG 114) was a multicentre randomised double-blind study involving 635 patients with AIDS or ARC and <3 months of prior zidovudine exposure. The results of this study (published as an abstract) showed 1-year survival to be significantly lower in the zalcitabine (2.25 mg/day) compared with the zidovudine (600 or 1200 mg/day) treatment group (68.4 *vs* 76.8%; p = 0.02).[110] Furthermore, in a subgroup analysis, zidovudine-treated patients were significantly less likely to require invasive procedures or hospitalisation and also experienced significantly fewer symptoms that interfered with daily activity and fewer days of disability during the first 48 weeks of follow-up.[111]

More favourable results have been reported with zalcitabine monotherapy in smaller studies. Substitution with zalcitabine was associated with a significant survival benefit at 12 months (p = 0.05) compared with substitution with didanosine, remaining on zidovudine or no nucleoside therapy in a retrospective analysis of 154 patients (CD4+ count <200 cells/μl) who were intolerant of or unresponsive to zidovudine monotherapy.[112] In study CPCRA 002, a multicentre, nonblind, randomised trial, zalcitabine was at least as effective as didanosine in delaying disease progression and death in 467 patients with advanced HIV disease (CD4+ count ≤300 cells/μl) who had failed to respond to or were intolerant of zidovudine monotherapy.[113] The results of ACTG 119, a nonblind, randomised trial which recruited 111 patients with extensive zidovudine exposure (≥48 weeks), showed that substitution with zalcitabine produced a small nonsignificant survival advantage (estimated 12-month survival rates 81 *vs* 75%) and a significantly (p < 0.05) slower reduction in CD4+ cell count at week 28 compared with continued zidovudine therapy.[114]

3.2 Combination Therapy

Initial studies evaluating combination antiretroviral therapy compared regimens comprising 2 nucleoside analogues (including zalcitabine) with antiretroviral monotherapy (table III). These included the 3 large clinical end-point studies, ACTG 175,[116], CPCRA 007[120] and Delta.[121] Subsequent to this, additional studies have evaluated 2- and 3-drug regimens comprising a nucleoside analogue plus a protease inhibitor or 2 nucleoside analogues plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Zalcitabine has been included as a component of regimens evaluated in some of these later studies

Table III. Summary of multicentre randomised double-blind trials evaluating oral zalcitabine (ZAL) as combination therapy in adults with HIV infection

Reference	Characteristics of pts (duration of follow-up)	No. of pts (disease stage)	Treatment regimen (mg/day)	Change in HIV RNA levels from baseline (log_{10} copies)	Change in CD4+ count from baseline (cells/μl)	No. of pts with disease progression[a] (%)	No. of deaths (%)
ACTG 155[115]	ZDV for ≥6mo; AIDS or SYM and CD4+ count ≤300 cells/μl, or ASY and CD4+ count ≤200 cells/μl (med 18mo)	285 (49 ASY)	ZAL 2.25		↓32%	123 (43)	51 (18)
		283 (54 ASY)	ZDV 600		↓32%	118 (42)	43 (15)
		423 (72 ASY)	ZAL 2.25 + ZDV 600		↓25%	164 (39)	78 (18)
ACTG 175[116]	ZDV-naive; CD4+ count 200-500 cells/μl (med 135wk)	267	ZAL 2.25 + ZDV 600		↑41[b††]	16 (6)[†]	9 (3)
		263	DID 400 + ZDV 600		↑63[b††]	20 (8)	11 (4)
		269	ZDV 600		↑14[b]	32 (12)	18 (7)
		268	DID 400		↑49[b††]	23 (9)	11 (4)
	ZDV-experienced; CD4+ count 200-500 cells/μl (med 147wk)	348	ZAL 2.25 + ZDV 600		↑13[b††]	60 (17)	31 (9)
		350	DID 400 + ZDV 600		↑40[b††]	45 (13)[†]	20 (6)[†]
		350	ZDV 600		↓22[b]	64 (18)	36 (10)
		352	DID 400		↑34[b††]	48 (14)	18 (5)[††]
ACTG 229[117]	ZDV for ≥4mo; CD4+ count 50-300 cells/μl (≤56wk)	100 (10 AIDS; 49 SYM; 41 ASY)	ZAL 2.25 + ZDV 600	↓0.1[c]	↓25%[c]	6 (6)	
		98 (13 AIDS; 52 SYM; 33 ASY)	ZAL 2.25 + ZDV 600 + SQV 1800	↓0.35[c‡‡]	0%[c‡‡]	3 (3)	
		99 (10 AIDS; 52 SYM; 37 ASY)	ZDV 600 + SQV 1800	↑0.3[c]	↓30%[c]	8 (8)	
BW 34, 225-02[118]	ZDV for <4wk; CD4+ count <300 cells/μl (48-72wk)	61 (20 AIDS; 26 ARC; 15 ASY)	ZAL 2.25 + ZDV 600	↓1.0[d††]	↑35[††]	26 (43)[e]	31 (51)[e]
		59 (10 AIDS; 24 ARC; 25 ASY)	DID 200 + ZDV 600	↓0.6[d††]	↑60[††]	20 (34)[e]	22 (37)[e]
		60 (19 AIDS; 24 ARC; 17 ASY)	ZDV 600	↓0.3[d]	↓25	26 (43)[e]	32 (53)[e]
CAESAR[119][f]	ZDV-experienced; CD4+ cell count 25-250 cells/μl (med 52wk)	475	LAM 300 + LOV 300[g]			38 (8)[‡‡‡]	13 (3)[‡‡‡]
		935	LAM 300[g]			80 (9)[‡‡‡]	22 (2)[‡‡‡]
		482	PI[g]			81 (17)	22 (5)
CPCRA 007[120]	77% pts ZDV-experienced [med 7mo]; AIDS or CD4+ count <200 cells/μl (med 35mo)	367 (127 AIDS)	ZAL 2.25 + ZDV 600		↑12.9[h††]	230 (63)	182 (50)
		363 (110 AIDS)	DID 400 + ZDV 600		↑19.2[h††]	226 (62)	176 (48)
		372 (112 AIDS)	ZDV 600		↓4[g]	244 (66)	191 (51)
Delta[121]	ZDV-naive (med 30mo)	706 (91 AIDS; 212 SYM; 403 ASY)	ZAL 2.25 + ZDV 600		↑67[b]	231 (33)[i]	107 (15)[j]
		718 (91 AIDS; 215 SYM; 412 ASY)	DID 400 + ZDV 600		↑80[b]	188 (26)[i]	93 (13)[j]
		700 (80 AIDS; 204 SYM; 416 ASY)	ZDV 600		↑30[b]	270 (39)	149 (21)
	ZDV for ≥3mo (med 30mo)	366 (66 AIDS; 119 SYM; 181 ASY)	ZAL 2.25 + ZDV 600		↑3[b]	175 (48)	121 (33)
		362 (56 AIDS; 136 SYM; 170 ASY)	DID 400 + ZDV 600		↑20[b]	165 (46)	103 (28)
		355 (58 AIDS; 110 SYM; 187 ASY)	ZDV 600		↓12[b]	178 (50)	126 (35)
M50003[122][f]	241 pts ZDV-naive; CD4+ count 300-500 cells/μl (105 pts 24mo)	129	ZAL 2.25 + ZDV 600		↑110		
		127	ZDV 600		↓36		

NUCA 3002[123]	ZDV for ≥6mo; CD4+ count 100-300 cells/μl (52wk)	86 (50 ASY)	ZAL 2.25 + ZDV 600	↓0.49	↓4.4	19 (22)	0
		84 (47 ASY)	LAM 300 + ZDV 600	↓0.43	↑38.5*	11 (13)	0
		84 (51 ASY)	LAM 600 + ZDV 600	↓0.47	↑22.5*	14 (17)	0
NV14256 [124]	ZDV for ≥16wk; CD4+ count 50-300 cells/μl (med 73wk)	314	ZAL 2.25	↓0.3	↓6.2	85 (27)	28 (9)
		318	SQV 1800	↓0.1	↓0.4	77 (24)	34 (11)
		308	ZAL 2.25 + SQV 1800	↓0.4‡	↑20.4‡	46 (15)k**	9 (3)k**

a New AIDS event or death.
b After 8wk.
c Up to 48wk.
d At 12wk. Serum HIV RNA levels after 48wk were below 4.6 log_{10} copies/ml for both combination therapies and returned to baseline values for monotherapy.
e Data from 154 patients followed long term (up to 4y).
f Abstract.
g Added to existing therapy comprising ZDV, ZDV + ZAL or ZDV + DID.
h After 2mo.
i Hazard ratio (95% confidence interval) *vs* ZDV: ZAL + ZDV 0.80 (0.67-0.96); DID + ZDV 0.63 (0.53-0.76).
j Hazard ratio (95% confidence interval) *vs* ZDV: ZAL + ZDV 0.68 (0.53-0.88); DID + ZDV 0.58 (0.45-0.75).
k Statistically significant for time to first AIDS event or death.
l Statistically significant for time to death.

Abbreviations and symbols: ARC = AIDS-related complex; ASY = asymptomatic; DID = didanosine; LAM = lamivudine; LOV = loviride; med = median; Pl = placebo; pts = patients; SQV = saquinavir; SYM = symptomatic but not AIDS; ZDV = zidovudine; ↑ indicates an increase; ↓ indicates a decrease; *$p \leq 0.05$ *vs* ZAL + ZDV; **$p \leq 0.01$ *vs* SQV; †$p \leq 0.05$, ††$p \leq 0.01$ *vs* ZDV; ‡$p \leq 0.001$ *vs* monotherapy; ‡‡$p \leq 0.05$ *vs* double combination therapy; ‡‡‡$p \leq 0.05$ *vs* placebo.

(table III), the results of which are discussed in sections 3.2.1 and 3.2.2.

3.2.1 Double Combination Therapy

Zalcitabine in Combination with Other Nucleoside Analogues

The results of initial comparative studies evaluating zalcitabine plus zidovudine combination therapy (ACTG 106[125] and BW 34,225-02[118]) reported a greater and more sustained increase in CD4+ cell count and more sustained decrease in p24 antigen levels with zalcitabine plus zidovudine than with zidovudine alone. Although not the primary end-point, long term clinical follow-up of 154 patients in study BW 34,225-02 revealed a greater delay in the development of an AIDS-defining event or death ($p = 0.022$) with combination therapy than with zidovudine monotherapy. The significantly greater prolongation of survival time ($p = 0.04$) and time to clinical disease progression and death ($p = 0.004$) reported with zidovudine plus didanosine compared with zidovudine plus zalcitabine in this study may have been attributable in part to the better baseline clinical and virological status of patients in the didanosine compared with the zalcitabine treatment group.[118]

ACTG 155 was the first major trial to compare zidovudine plus zalcitabine combination therapy with zidovudine or zalcitabine monotherapy using clinical efficacy as the primary end-point.[115] In this study, which involved 991 zidovudine-pretreated patients with advanced disease, no significant difference in time to disease progression or death was reported between those receiving zidovudine plus zalcitabine combination therapy and those treated with zidovudine monotherapy. A planned subgroup analysis revealed the combination regimen to be significantly ($p = 0.029$) more effective in terms of disease progression and death in patients with a CD4+ count of ≥150 cells/μl but no significant difference was reported in patients with more advanced disease (<150 cells/μl). Results from ACTG 193A provide further data to suggest that combination therapy with zidovudine plus zalcitabine is not the preferred treatment option for

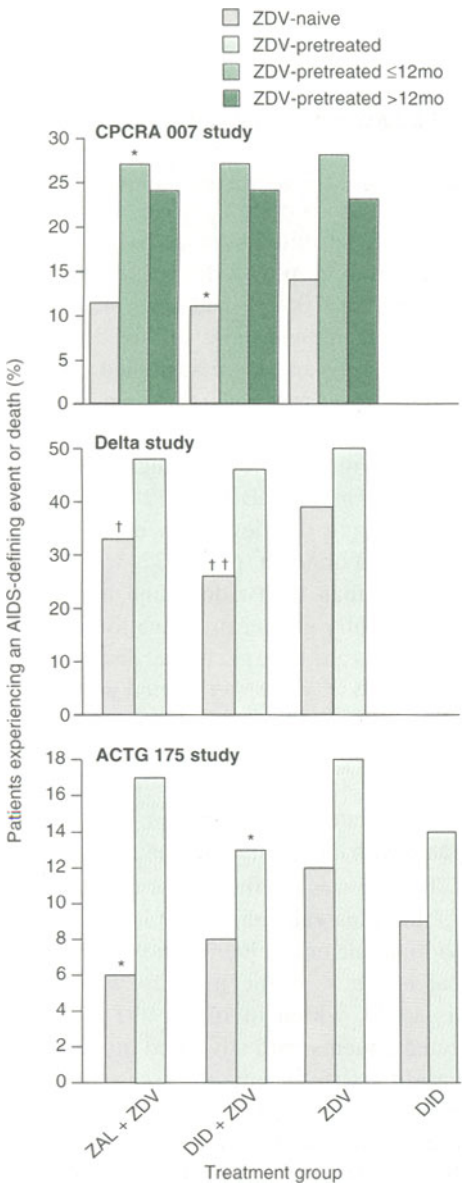

Fig. 1. Percentage of patients who experienced an AIDS-defining event or death in 3 large, randomised multicentre studies [ACTG 175 (n = 2467),[116] Delta (n = 3207)[121] and CPCRA 007 (n = 1102)[120]]. Patients with advanced HIV infection were randomised to receive zidovudine (ZDV) 600 mg/day plus zalcitabine (ZAL) 2.25 mg/day or didanosine (DID) 400 mg/day, or ZDV or DID monotherapy. *Symbols*: *p < 0.05 *vs* ZDV monotherapy, †hazard ratio 0.80(95% CI 0.67-0.96) *vs* ZDV monotherapy, ††hazard ratio 0.63(95% CI 0.53-0.76) *vs* ZDV monotherapy and hazard ratio 0.79(95% CI 0.65-0.96) *vs* ZDV + ZAL.

patients with late stage disease (CD4+ count ≤50 cells/μl).[126]

The 3 clinical end-point studies, ACTG 175, CPCRA 007 and Delta recruited large numbers of zidovudine-naive and zidovudine-experienced patients with relatively late-stage disease. All 3 trials were randomised multicentre double-blind studies, included a follow-up period of >2 years and enrolled more than 1000 patients.

Study ACTG 175 recruited the greatest number of zidovudine-experienced patients (n = 1400) and compared 4 different regimens, zidovudine or didanosine monotherapy, zidovudine plus zalcitabine and zidovudine plus didanosine (table III).[116] For the antiretroviral-naive patients (n = 1067), progression to the primary end-point (≥50% decline in CD4+ cell count, occurrence of an AIDS defining event or death) was significantly more frequent with zidovudine monotherapy (23%) than with treatment with zidovudine plus zalcitabine (10%; $p < 0.001$), zidovudine plus didanosine (14%; $p = 0.003$) or didanosine alone (17%; $p = 0.023$). When the clinical end-points of AIDS or death were considered in aggregate, only zidovudine plus zalcitabine therapy was associated with a significant reduction in the number of patients experiencing disease progression compared with zidovudine monotherapy (6 *vs* 12%; $p = 0.016$) (fig. 1); the corresponding results for zidovudine plus didanosine and didanosine monotherapy were 8% ($p = 0.082$) and 9% of patients ($p = 0.11$), respectively.

For previously treated patients, progression to the primary end-point in this study was significantly lower with the combination of zidovudine plus zalcitabine (27%) or didanosine (22%), or didanosine alone (26%) compared with zidovudine monotherapy (38%; $p < 0.001$). However, only zidovudine plus didanosine had a significant clinical benefit over zidovudine monotherapy when the clinical end-points of AIDS or death were considered in aggregate in this patient group (13 *vs* 18%; $p = 0.025$).

In CPCRA 007, which enrolled 1102 mainly zidovudine-experienced patients, treatment with

zidovudine plus zalcitabine or didanosine did not significantly delay disease progression or prolong survival compared with zidovudine alone (table III).[120] After a median follow-up time of 35 months, the relative risk of disease progression or death compared with zidovudine therapy was 0.92 [95% confidence interval (CI) 0.76 to 1.10] and 0.86 (95% CI 0.71 to 1.03) for treatment with zidovudine plus zalcitabine and zidovudine plus didanosine, respectively. However, in a subgroup analysis, combination therapy with zidovudine plus zalcitabine significantly reduced the rate of disease progression or death compared with zidovudine alone in patients who had been previously treated with zidovudine for ≤12 months ($p < 0.05$; relative risk 0.72; 95% CI 0.54 to 0.96) [fig. 1]. No significant difference was reported between zidovudine plus didanosine and zidovudine alone in this patient group. However, the zidovudine plus didanosine regimen did produce a significant reduction in disease progression or death compared with zidovudine monotherapy in zidovudine-naive patients ($p < 0.05$; relative risk 0.57; 95% CI 0.36 to 0.90). A significant difference was not reported for zalcitabine plus zidovudine combination therapy in this respect.

The results of the European/Australian Delta trial, the largest (n = 3207), most powerful study available, provided evidence of the superior efficacy of zidovudine plus zalcitabine or didanosine compared with zidovudine monotherapy in terms of survival and progression to AIDS in antiretroviral-naive patients (table III).[121] Compared with zidovudine alone, a relative reduction in mortality (based on hazard ratios) of 32% ($p = 0.003$) for zidovudine plus zalcitabine and 42% ($p < 0.0001$) for zidovudine plus didanosine therapy was reported. However, in zidovudine-experienced patients there was no evidence of a direct benefit of adding zalcitabine to therapy compared with continuing with zidovudine alone; only zidovudine plus didanosine combination therapy produced a survival benefit compared with zidovudine monotherapy in this patient group. The relative reduction in mortality was 23% for zidovudine plus didanosine ($p = 0.05$) and 9% for zidovudine plus zalcitabine ($p = 0.47$). Figure 1 shows the percentage of patients experiencing a new AIDS event or death in each of the 3 treatment groups. Although not the primary comparison, Delta also provided some information on the comparative efficacy of the 2 combination regimens. Notably, treatment with zidovudine plus didanosine produced a significant delay in the development of a new AIDS event or death for the study population overall and a significant delay in progression to AIDS or death compared with zidovudine plus zalcitabine in zidovudine-naive patients without AIDS at study entry. However, there was no significant difference between the 2 treatment groups in terms of mortality rate.

In another double-blind multicentre study, M50003, treatment with zidovudine plus zalcitabine was significantly ($p < 0.001$) better than zidovudine monotherapy at maintaining CD4+ cell count above baseline at 24 months in patients with little or no prior antiretroviral therapy (90 *vs* 52.4% of patients; $p < 0.001$).[122] However, this study was discontinued prematurely following the results of ACTG 175 and Delta, which showed a significant improvement in survival and disease progression with combination therapy in antiretroviral-naive patients.

Data from large observational[127] and longitudinal cohort[128] studies also demonstrated a significant survival benefit with combination therapy with zidovudine plus zalcitabine or didanosine compared with zidovudine monotherapy.

Zidovudine plus zalcitabine therapy has also been compared with combination regimens comprising zidovudine plus the nucleoside reverse transcriptase inhibitor lamivudine (300 or 600 mg/day). In study NUCA 3002,[123] which recruited 254 zidovudine-experienced patients, a significantly ($p < 0.05$) greater increase in mean CD4+ cell count was reported for the low dose (+38.5 cells/μl) and high dose (+22.6 cells/μl) lamivudine groups compared with the zalcitabine group (–4.4 cells/μl) after 52 weeks of follow-up. However, suppression of plasma HIV RNA levels

was similar for all groups (table III). Triple combination therapy with zalcitabine, zidovudine and lamivudine has also been evaluated in a recent study (section 3.2.2).

A preliminary evaluation of zalcitabine and zidovudine combination therapy in the treatment of 4 patients with HIV-associated dementia demonstrated a reversal of neurocognitive dysfunction and a marked reduction in serum and CSF HIV RNA titres.[109]

Zalcitabine in Combination with a Protease Inhibitor

The reported *in vitro* synergy between zalcitabine and the protease inhibitor saquinavir and the non-overlapping toxicity and resistance profiles of these 2 drugs has led to evaluation of their efficacy in combination. To date, one study (NV14256) has evaluated the efficacy of a 2-drug regimen comprising zalcitabine plus saquinavir (table III) while other studies have evaluated 3-drug regimens including zalcitabine plus saquinavir or the protease inhibitor ritonavir (section 3.2.2).

Study NV14256, a multicentre double-blind study, randomised 940 HIV-infected zidovudine-experienced patients to receive zalcitabine plus saquinavir or either agent alone (table III). The final results from this study have not yet been published; however, data on disease progression and mortality are available.[124] An intent-to-treat analysis of patients with a median follow-up of 73 weeks showed the time to the first AIDS-defining event or death to be significantly longer for patients treated with the combination regimen than for those treated with saquinavir monotherapy ($p = 0.0043$; log rank analysis). A 74% reduction in mortality with saquinavir plus zalcitabine compared with saquinavir monotherapy (9 *vs* 34 deaths) provided further evidence of the benefit of this combination regimen in zidovudine-experienced patients. This benefit was statistically significant according to an intent-to-treat log-rank analysis of the time to death ($p = 0.0001$). A significantly greater ($p = 0.0001$) and more sustained increase in CD4+ cell count and decrease in viral load was also reported with saquinavir plus zalcitabine than with either agent alone. Notably, no significant difference in clinical end-points was reported between saquinavir or zalcitabine monotherapy.

3.2.2 Triple Combination Therapy

Multidrug combination therapy is potentially the most viable therapeutic option for the successful treatment of HIV infection, since it is potentially associated with an increase in antiviral activity and a greater delay in the emergence of drug resistance compared with monotherapy. The results of *in vitro* studies, demonstrating greater activity with triple combination therapy than with 2-drug regimens,[129] are now supported by data from surrogate marker and early clinical end-point studies. Zalcitabine has been evaluated as a component of triple combination regimens including the protease inhibitors saquinavir or ritonavir plus zidovudine or the nucleoside analogue lamivudine plus zidovudine in predominantly zidovudine-experienced patients with advanced disease.

Study ACTG 229 was designed to assess the effect of triple combination therapy with zidovudine, zalcitabine and saquinavir on surrogate marker activity in 297 heavily zidovudine-experienced patients. Notably, changes in absolute CD4+ cell count and quantitative HIV titre to week 48 of treatment were reported to be significantly superior with the 3-drug combination compared with either double therapy (zidovudine plus saquinavir or zalcitabine) [table III].[117] Although clinical disease progression and survival were not primary end-points, 17 patients developed an AIDS-defining illness or died during the study, 3 in the 3-drug group, 8 in the saquinavir plus zidovudine group and 6 in the zalcitabine plus zidovudine group. An analysis of ranked quality-of-life scores obtained at baseline and week 20 also revealed a trend in favour of the triple combination regimen for an improvement in functional and psychological health and work/social functioning.[130]

Although inhibition of zalcitabine phosphorylation by lamivudine has been reported *in vitro* (section 1.2), 2 studies have demonstrated a beneficial effect from adding lamivudine to combination therapy comprising zidovudine plus zalcitabine. In a

nonblind, randomised trial with a 6-month follow-up,[131] 46 patients pretreated with zidovudine plus zalcitabine for ≥6 months were randomised to receive either zidovudine, zalcitabine and lamivudine (n = 15), zidovudine and lamivudine (n = 15) or to continue with existing zidovudine plus zalcitabine therapy (n = 16) [control group]. Compared with baseline, mean CD4+ cell count increased significantly in the triple therapy (+49.5 cells/μl; p = 0.0012) and zidovudine plus lamivudine (+33.1 cells/μl; p = 0.021) treatment arms but decreased in the control group (–21.3 cells/μl) over 24 weeks. A corresponding decrease in mean plasma HIV-1 RNA levels from baseline was reported for both zidovudine plus lamivudine (–0.15 log copies/ml) and zidovudine plus zalcitabine plus lamivudine (–0.45 log copies/ml; p = 0.003), while an increase was reported for the control group (+0.36 log copies/ml; p = 0.024).

The CAESAR study evaluated the benefit of adding lamivudine ± loviride to ongoing antiretroviral therapy (zidovudine plus zalcitabine or didanosine or zidovudine monotherapy) for 52 weeks in 1892 patients with advanced HIV infection.[119] The recently reported results of an interim analysis of this study showed that in comparison with placebo, addition of lamivudine ± loviride to existing antiretroviral therapy significantly reduced disease progression (8 and 9 *vs* 17%; p < 0.0001) and mortality rates (2.4 and 2.7 *vs* 4.6%; p = 0.012). Further analysis revealed a 55% reduction in disease progression in the lamivudine-containing arms in patients who entered the trial on zidovudine monotherapy and a 49% reduction in patients who entered the trial on zidovudine plus zalcitabine or didanosine.

Impressive immunological benefits were demonstrated in a pilot study evaluating a regimen comprising zalcitabine plus zidovudine in combination with the protease inhibitor ritonavir (1200 mg/day) as first line therapy in 29 HIV-infected adults (CD4+ count <250 cells/μl).[132] After 9 months of treatment the mean titre of HIV RNA and the mean number of infectious blood cells had decreased by 2.0 log copies/ml plasma and 2.44 log cells per 10^7 peripheral blood mononuclear cells, respectively. This was accompanied by a corresponding increase in mean CD4+ cell count (+140 cells/μl).

Studies evaluating zalcitabine in combination with zidovudine and thymostimulin,[133] zidovudine and interferon-α[134] and zidovudine and delavirdine[135] have also been conducted. Preliminary evaluation of a 4-drug regimen comprising zalcitabine, zidovudine, didanosine and interferon-α produced promising results in terms of a reduction in HIV plasma RNA and an increase in CD4+ cell count.[136]

3.3 Paediatric Use

Study ACTG 138 evaluated the efficacy of zalcitabine 0.015 and 0.03 mg/kg/day in 170 HIV-infected children with symptomatic disease who were refractory to or intolerant of zidovudine.[137] p24 antigen levels were reduced at 36 weeks for 38% of the children evaluated. Combination therapy comprising zalcitabine plus zidovudine has also been evaluated in children.[81] 13 patients received a regimen of zalcitabine 0.12 mg/kg/day for 7 days alternating with zidovudine 720 mg/m^2/day for 21 days. Of these patients, 11 experienced weight gain and 7 an increase in CD4+ cell count and a >10% increase in the CD4 to CD8 ratio. In a small study, zalcitabine salvage therapy improved metabolic rates and nutritional parameters in children with advanced HIV disease.[138] However, alternating combination therapy with zidovudine and zalcitabine was unable to prevent the development of zidovudine resistance in HIV-1 isolates from children.[139]

3.4 Pharmacoeconomic Considerations

In view of the potential increase in drug costs associated with the use of combination antiretroviral regimens, a model was developed to assess the comparative cost-effectiveness of adding zalcitabine to antiretroviral therapy.[140] The model was based on data derived from clinical studies (ACTG 106,[141] ACTG 114[141] and BW 34,225-02[60]) demonstrating a sustained improvement in CD4+

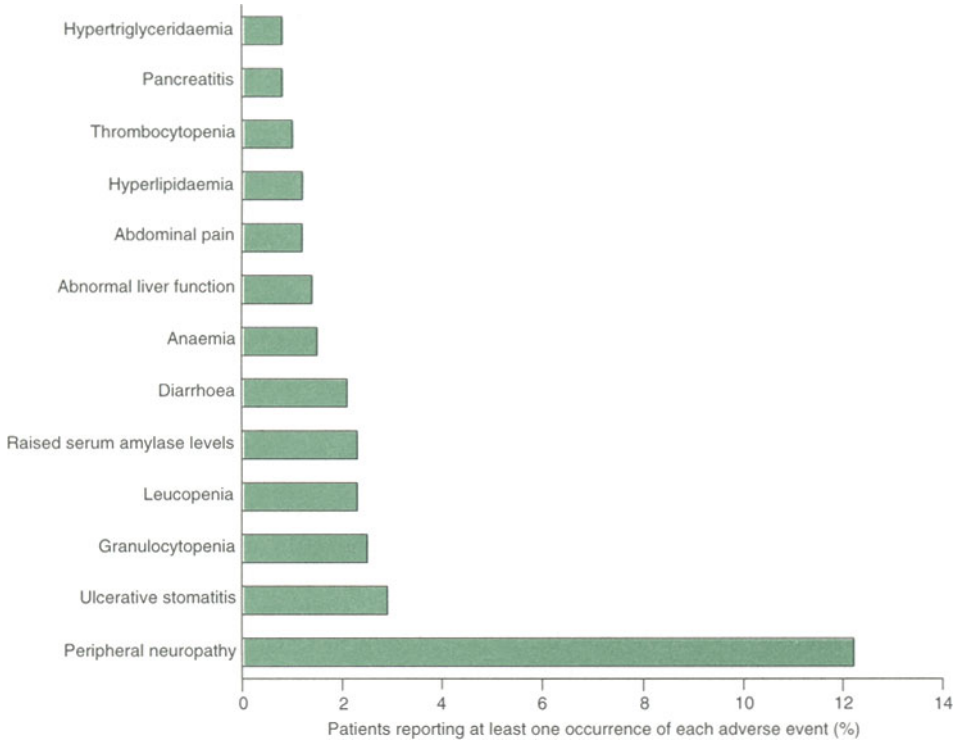

Fig. 2. Incidence of adverse events (all grades) at least possibly related to zalcitabine therapy and reported in ≥0.8% of patients (n = 517) participating in the zalcitabine Expanded Access Programme.[142]

cell count in patients treated with zalcitabine plus zidovudine. The model predicted that the use of this antiretroviral regimen for 1 year was a cost-effective treatment option for patients with a CD4+ count <300 cells/μl. Compared with zidovudine monotherapy, combination therapy improved survival by 0.09 to 0.11 life-years per patient and this was associated with a modest cost increase of 1181 to 1764 European Currency Units per patient depending upon the country studied. The results of this study, however, are limited by the assumption that CD4+ cell count is a good on-therapy marker of disease progression and survival.

4. Tolerability

4.1 Zalcitabine Monotherapy

Since the previous zalcitabine review in *Drugs*,[1] additional data have been published on the tolerability of this agent, including the results of a European Expanded Access Programme (EAP).[142] This programme provided data on 517 patients with AIDS or ARC who received zalcitabine 2.25 mg/day; approximately 50% of patients received the drug for >12 weeks. All patients recruited to the study were either no longer able to tolerate zidovudine, had not responded to zidovudine or were ineligible to receive the drug. The adverse events (all grades) experienced by ≥0.8% of patients and at least possibly related to zalcitabine therapy are summarised in figure 2.

Peripheral neuropathy, the most frequent adverse event, developed in 63 patients (12.2%); other adverse events occurred with a frequency of <3.0% and included ulcerative stomatitis, granulocytopenia and leucopenia; pancreatitis developed in fewer than 1% of patients. The overall incidence of severe adverse events was 2.1% and included

pancreatitis (0.8% of patients), peripheral neuropathy (0.4%), hyperamylasaemia (0.2%), thrombocytopenia (0.2%), neutropenia (0.2%), abnormal liver function (0.2%) and ulcerative stomatitis (0.2%).

These results are generally in accordance with those of 2 recently published large comparative studies (ACTG 155 and CPCRA 002) which included an assessment of the tolerability profile of zalcitabine monotherapy; the incidence of grade III or IV[113] or common severe or worse adverse effects[115] were reported in these studies. Peripheral neuropathy and haematological adverse events were generally the major toxicities associated with zalcitabine, although abnormal liver function and cutaneous or allergic reactions were reported more frequently than in the European EAP study (table IV).

As with other antiretroviral agents, the incidence of adverse events with zalcitabine has been shown to progressively increase with a decline in CD4+ cell count.[142,143]

4.1.1 Peripheral Neuropathy

Peripheral neuropathy is the major dose-limiting adverse event associated with zalcitabine treatment,[144] occurring in 12 to 46% of patients receiving zalcitabine 1.125 to 2.25 mg/day.[112-115,142,145-147] Initial symptoms are predominantly sensory with distal dysaesthesia, pain and numbness. Abnormal sural nerve conduction is frequently evident with an impaired sensation of vibration, pain and temperature.[148] Available data clearly suggest that this adverse event is dose-related both in terms of incidence and severity and progression of symptoms.[1,144] However, zalcitabine-induced peripheral neuropathy is slowly reversible on cessation of drug therapy and several patients have been successfully rechallenged with a lower dosage of zalcitabine.[149]

Significant risk factors for the development of zalcitabine-induced neuropathy include diabetes mellitus and a low serum cobalamin level (<148 pmol/L); a weak correlation between the development of this condition and weight loss, heavy alcohol consumption and/or a history of symptoms of

Table IV. Summary of adverse events [no. of patients (%)] in 2 large comparative studies of zalcitabine (ZAL) in zidovudine (ZDV)-experienced patients with advanced HIV disease

Adverse event	CPCRA 002[113]a		ACTG 155[115]b		
	ZAL (n = 237)	DID (n = 230)	ZAL (n = 285)	ZDV (n = 283)	ZAL + ZDV (n = 423)
Peripheral neuropathy	69 (29.1)	33 (14.3)	18 (6)	12 (4)	25 (6)
Abnormal liver function	24 (10.0)	20 (8.6)	16 (6)	24 (8)	25 (6)
Neutropenia	18 (7.6)	21 (9.1)	26 (9)	49 (17)	82 (19)
Anaemia or haemoglobinaemia	15 (6.3)	14 (6.1)	13 (5)	14 (5)	35 (8)
Cutaneous/allergic reaction	17 (7.1)	13 (5.6)	6 (2)	4 (1)	6 (1)
Abdominal pain	7 (2.9)	16 (6.9)			
Diarrhoea	9 (3.8)	48 (20.8)			
Nausea or vomiting	21 (8.9)	35 (15.2)	4 (1)	7 (2)	4 (1)
Fever	8 (3.4)	13 (5.6)	12 (4)	23 (8)	17 (4)
Headache	10 (4.2)	9 (3.9)	5 (2)	5 (2)	10 (2)
Fatigue	9 (3.8)	6 (2.6)	5 (2)	7 (2)	19 (4)
Muscle weakness	9 (3.8)	8 (3.5)			
Oral lesions or stomatitis	8 (3.4)	0 (0)	11 (4)	2 (1)	4 (1)
Hyperamylasaemia	9 (3.8)	13 (5.6)			
Pancreatitis	0 (0)	4 (1.7)	9 (3)	4 (1)	8 (2)

a Incidence of grade III or IV adverse events reported.

b Incidence of common severe or worse adverse events reported.

Abbreviation: DID = didanosine.

peripheral nerve dysfunction and peripheral neuropathy has also been reported.[145,146] Notably, in the European EAP study, zalcitabine-associated peripheral neuropathy was more likely in patients with a baseline diagnosis of AIDS and a CD4+ count ≤50 cells/μl.[142]

Two case reports have also highlighted the development of zalcitabine-associated ototoxicity (attributable to neurotoxic effects on the eighth cranial nerve) which resolved on discontinuation of the drug.[150,151] A case of acute paralysis of the serratus muscle has also been reported in a patient treated with zalcitabine for 2 months.[152]

Anecdotal reports suggest zalcitabine is a well tolerated alternative to zidovudine in patients with zidovudine-induced myopathy.[153]

4.1.2 Oral Stomatitis

Oral stomatitis is a frequently reported adverse effect associated with zalcitabine therapy which may resolve with continuing administration of the drug. It developed in 3 to 4% of patients receiving zalcitabine monotherapy in 3 large studies.[113,115,142] In a cross-sectional study involving 338 patients, the reported incidence of oral ulceration was significantly higher for zalcitabine-treated than for zidovudine- or didanosine-treated patients (29 *vs* 15%; p = 0.018).[154] Another study reported no significant association between the use of zalcitabine plus zidovudine combination therapy and the development of oral ulcers.[155]

An isolated case of oesophageal ulceration[156] and a distinctive dose-dependent maculopapular rash associated with oral ulceration and occasionally fever[157,158] have been described after zalcitabine therapy.

4.1.3 Other Adverse Effects

Erythema multiforme[159] and hypersensitivity syndrome[160] associated with zalcitabine therapy have been reported anecdotally. Severe rash and hepatotoxicity associated with the use of zidovudine and zalcitabine for needlestick injuries also developed in 2 patients.[161]

Although the pancreas is often affected in patients with HIV infection, the most significant cause of pancreatic dysfunction in this setting is drug-induced disease.[162] However, the pathophysiological mechanisms involved in the development of drug-induced pancreatitis are incompletely understood. Pancreatitis appears to be a rare but serious complication of zalcitabine therapy[163] which has mostly been reported to occur with an incidence of <1% in large studies.[112,113,142] Elevated serum amylase levels have also been reported in a small number of patients treated with zalcitabine (0.2 to 3.8%).[113,142]

Despite concerns in recent years regarding a possible association between the incidence of lymphoma and the use of zalcitabine therapy, clinical trial data published to date suggest no significant correlation between the rate of lymphoma and the inclusion of zalcitabine in antiretroviral regimens.[164] Instead, the development of lymphoma in HIV-infected patients appears to be attributable to prolonged immunodeficiency associated with the disease rather than to the use of antiretroviral therapy.

Paediatric tolerability data for zalcitabine are limited. In an early investigation, rash and mouth sores were significant events during an initial 8-week period in which zalcitabine 0.015 to 0.04 mg/kg was administered every 6 hours.[81] However, in study ACTG 138, which compared the long term tolerability and efficacy of zalcitabine 5 or 10 μg/kg administered every 8 hours, 5 cases of peripheral neuropathy were reported among 170 children (median age 5.3 years).[137]

4.2 Combination Therapy

A recent international study (M50002) involving 561 patients found zalcitabine plus zidovudine combination therapy to be well tolerated by both zidovudine-naive and zidovudine-experienced patients during a 12-month follow-up period.[165] However, peripheral neuropathy, neutropenia and anaemia were more common in patients with a CD4+ count ≤100 cells/μl and/or a prior AIDS-defining event.

The results of study ACTG 155, which compared zidovudine or zalcitabine monotherapy with a combination of both agents, demonstrated no sta-

tistically significant difference in the overall incidence of severe adverse events between the 3 treatment groups.[115] However, severe neutropenia was more common in the zidovudine monotherapy and combination therapy arms (17 to 19% *vs* 9% with zalcitabine monotherapy; p = 0.0005) whereas moderate or severe peripheral neuropathy was more common in the zalcitabine monotherapy and combination therapy arms (22 to 23% *vs* 13% with zidovudine monotherapy; p = 0.005). In addition, the incidence of peripheral neuropathy was 34% with zalcitabine monotherapy compared with only 4% for patients treated with zidovudine alone ($p < 0.03$); however, there was no significant difference in this variable between patients receiving zalcitabine monotherapy and zalcitabine plus zidovudine combination therapy.[145]

In both ACTG 175 and CPCRA 007, the incidence of haematological abnormalities (anaemia and neutropenia) was higher for patients treated with zidovudine plus zalcitabine than for the comparative treatment groups. In ACTG 175 these events occurred in 10% of patients treated with zidovudine plus zalcitabine, which was significantly higher ($p < 0.001$) than in the other 3 treatment groups (zidovudine plus didanosine, or zidovudine or didanosine monotherapy).[116] In CPCRA 007 the incidence of haematological adverse events for zidovudine plus zalcitabine was 13.3 versus 11.5% for patients treated with zidovudine plus didanosine or zidovudine monotherapy.[120] Severe peripheral neuropathy was also reported to occur more frequently during treatment with zalcitabine plus zidovudine than during treatment with zidovudine monotherapy or zidovudine plus didanosine in both Delta (5 *vs* 1 to 2%) and CPCRA 007 (15 *vs* 7%).[120,121] In contrast, gastrointestinal symptoms were reported less frequently with zidovudine plus zalcitabine than with zidovudine plus didanosine.[120,121]

Tolerability data from studies NV14256 and ACTG 229 suggest that the combined use of zalcitabine with saquinavir does not alter the incidence or severity of adverse effects associated with the use of either drug alone.[117,124] In NV14256, the incidence of peripheral neuropathy in the zalcitabine and saquinavir plus zalcitabine groups was comparable, 21 and 20%, respectively.[124]

5. Drug Interactions

Patients with HIV infection frequently receive multiple drug therapy comprising both antiretroviral agents and drugs for the prophylaxis and/or treatment of opportunistic infections; the potential for drug-drug interactions in this patient group is therefore high. The drug interaction potential of antiretroviral agents has been previously reviewed by several authors.[167-169]

Because renal excretion of unchanged zalcitabine is the primary route of zalcitabine elimination in humans (section 2.2), the concomitant use of potentially nephrotoxic agents may have important clinical implications. For example, the aminoglycosides, amphotericin and foscarnet may potentially augment plasma zalcitabine concentrations and increase the incidence of zalcitabine-associated adverse effects, most notably peripheral neuropathy.[167-169] Concomitant administration of cimetidine, probenecid or trimethoprim has also been reported to reduce the renal clearance of zalcitabine with inhibition of renal tubular secretion postulated as the most probable mechanism.[170-172]

Caution should be exercised if zalcitabine is coadministered with other drugs that can cause peripheral neuropathy; these include dapsone, disulfiram, isoniazid, pentamidine, metronidazole, stavudine and didanosine. Patients should be carefully monitored for signs of peripheral neuropathy and treatment should be promptly discontinued if the condition develops. One patient who had been withdrawn from treatment with zalcitabine plus zidovudine experienced worsening of neuropathic symptoms upon subsequent administration of didanosine.[173] Severe left ventricular hypokinesis has also been reported during zalcitabine therapy following didanosine treatment.[174] Because of the increased risk of severe pancreatitis associated with the concomitant use of pentamidine and zalcitabine, the combined use of these 2 agents should be avoided.[167,169]

In view of the differing elimination pathways of zalcitabine, saquinavir and zidovudine, pharmacokinetic drug interactions between these 3 agents are considered unlikely.[168] In addition, significant pharmacokinetic interactions have not been reported during combination therapy with zalcitabine and nevirapine.[175]

The coadministration of aluminium hydroxide/magnesium hydroxide antacid mixture resulted in a 25% reduction in the bioavailability of zalcitabine and for this reason zalcitabine should not be administered concurrently with this antacid.[170] Zalcitabine has been reported to significantly decrease the clearance:bioavailability ratio of dapsone and increase this ratio for isoniazid.[176,177]

6. Dosage and Administration

Zalcitabine is administered orally as tablets which are available as 0.375 and 0.75mg formulations. The recommended dosage regimen for zalcitabine and zidovudine combination therapy is zalcitabine 0.75mg and zidovudine 200mg administered every 8 hours. Similarly, zalcitabine 0.75mg 3 times daily is recommended for use in combination with saquinavir or other approved protease inhibitors.[177] There are currently no recommended dosage schedules for the use of zalcitabine as a component of triple combination therapy, although zalcitabine 2.25mg/day has been used in clinical trials.

Zalcitabine dosage reduction to 0.75mg twice daily and 0.75mg once daily is recommended in adults and adolescents (age >13 years) with a CL_{CR} of 0.6 to 2.4 L/h (10 to 40 ml/min) and <0.6 L/h (<10 ml/min), respectively.[92]

Patients receiving zalcitabine therapy should be closely monitored for signs and symptoms of peripheral neuropathy; if these develop, zalcitabine therapy should be stopped until the associated signs and symptoms become at least mild in nature and only then reintroduced at a dose of 0.375mg every 8 hours. Permanent cessation of therapy may be necessary if severe symptoms develop or if the condition progressively worsens. Serum amylase levels should be monitored in individuals receiving zalcitabine therapy who have a history of elevated amylase levels, pancreatitis or alcohol abuse or who are receiving parenteral nutrition.[92]

Close haematological monitoring for signs of severe anaemia or granulocytopenia is necessary in zalcitabine recipients with poor bone marrow reserve, particularly in patients with advanced HIV disease. In the event of significant haematological toxicities (haemoglobin <7.5 mg/dl or >25% reduction from baseline; and/or granulocyte count <750 cells/μl or >50% reduction from baseline) interruption of treatment may be necessary until evidence of bone marrow recovery is seen.[92]

7. Place of Zalcitabine in the Management of HIV Infection

Until recently, zidovudine monotherapy was considered to be the standard first-line treatment for patients with HIV infection. However, the development of drug-resistant viral strains and incomplete suppression of viral replication have largely limited the extent and duration of response to monotherapy with this agent.[129] Over the past 18 months important advances have been made in the treatment of HIV infection, partly attributable to the development of several new and effective drugs and also to the publication of the results of a number of important clinical end-point studies demonstrating the clear benefits of combination antiretroviral therapy over monotherapy. For these reasons, monotherapy with any nucleoside analogue, including zalcitabine, is no longer considered to be an acceptable standard for the treatment of HIV infection; combination antiretroviral therapy is now established as the optimal approach.

The 3 large clinical end-point studies, CPCRA 007, ACTG 175 and Delta, have now firmly established that combination therapy with zidovudine plus zalcitabine or didanosine improves survival, delays disease progression and is associated with an improvement in viral load and CD4+ cell count compared with zidovudine monotherapy.[116,120,121] Despite some evidence of a greater benefit with zidovudine plus didanosine, the results of these studies do not definitively demonstrate that combi-

nation therapy with zidovudine plus didanosine is significantly better than zidovudine plus zalcitabine. Data from these studies also suggest a greater clinical benefit with combination therapy in zidovudine-naive patients than in zidovudine-pretreated patients. However, the lack of a significant difference in survival between these 2 patient groups in the largest, most powerful study, Delta, precludes any firm conclusions in this respect. Nevertheless, zalcitabine in combination with zidovudine does appear to be more effective in patients with limited prior zidovudine exposure. Furthermore, because of their differing tolerability profiles, zalcitabine and zidovudine are considered to be suitable agents for use in combination. Combination therapy with these agents has generally been associated with a tolerability profile comparable to that of either drug alone, although a significant increase in the incidence of haematological toxicity with zidovudine plus zalcitabine compared with zidovudine monotherapy was reported in one study.[116]

The publication of additional data in recent months has further advanced the therapeutic management of patients with HIV infection and led to the general consensus that the combined use of 2 nucleoside analogues such as zidovudine plus zalcitabine or didanosine does not represent optimal therapy for the treatment of HIV infection. For these reasons, current standard care is now moving towards the combined use of 1 or 2 nucleoside analogues with a protease inhibitor. This trend is highlighted in the recent guidelines from the International AIDS Society, which recommend the combined use of zalcitabine, didanosine or lamivudine with zidovudine (± a protease inhibitor) as initial therapy and the use of at least 2 new drugs such as 1 or 2 nucleoside analogues and a protease inhibitor for previously treated patients.[178] Notably, recent surrogate marker and clinical data have established the clinical efficacy of zalcitabine plus the protease inhibitor saquinavir in zidovudine-experienced patients. Furthermore, compared with zalcitabine or saquinavir monotherapy, the combined use of these agents does not appear to produce a significant change in tolerability profile. Additional studies have also demonstrated the utility of zalcitabine in combination with the protease inhibitor ritonavir or the nucleoside analogue lamivudine as components of 3- and 4-drug regimens.

Notably, available resistance data for zalcitabine are favourable, with resistance developing less frequently than during zidovudine therapy. Furthermore, the early use of zalcitabine in the treatment cycle does not appear to limit the utility of subsequent therapeutic options.

In view of current trends in clinical practice and available clinical trial data, the main place for zalcitabine in the treatment of HIV infection is likely to be as a component of triple combination regimens including zidovudine and a protease inhibitor or as the second agent in initial double therapy involving zidovudine. In these roles, zalcitabine will need to compete with other nucleoside analogues such as didanosine and lamivudine.[178] The choice of which nucleoside analogue to use should be based not only on efficacy but also on several other factors including tolerability, drug resistance patterns and potential for limiting future therapeutic options. In addition, ease of administration, drug cost and individual clinician and patient preference will also play an important role in drug selection.

In conclusion, available data support the inclusion of zalcitabine as a component of initial double combination regimens with zidovudine or as part of triple combination therapy with zidovudine plus a protease inhibitor. It is anticipated that ongoing and future trials will provide definitive data to aid selection of the optimal treatment regimen for patients with HIV infection.

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