

Failure to maintain high-dose treatment regimens during long-term use of zidovudine in patients with symptomatic human immunodeficiency virus type 1 infection

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Abstract

Long-term tolerance of zidovudine treatment was retrospectively analysed in 97 patients with AIDS or AIDS-related complex. After one year of treatment 68% and after two years 87% of the patients had had at least one dose adjustment during their course of therapy. Myelotoxicity was the most common cause (58% of all cases) of dose reductions and therapy interruptions (dose adjustments). At the time of the first dose adjustment 33 patients (34%) were suffering from anaemia (Hb < 6.0 g/dl), 20 patients (21%) from leukopenia (leukocytes < 1.5×10^9), and 10 patients (10%) from thrombocytopenia (thrombocytes < 75×10^9). Fifty-six patients (57%) needed one or more blood transfusions during therapy. The median time from the start of therapy to the time of the first dose adjustment was 14 (range: 2-64) weeks in patients who had a first dose adjustment because of anaemia without co-existing leukopenia or thrombocytopenia, and 37 (range: 6-85) weeks in patients who had a first dose adjustment because of leukopenia without co-existing anaemia or thrombocytopenia ($p = 0.01$). Peripheral blood CD4 positive lymphocyte counts $\leq 100/\text{mm}^3$, anaemia, and CDC classification IV-C1 at the start of treatment were associated with a need for an early dose modification or blood transfusion rather than the need for dose modification per se.

Zidovudine (3'-azido-3'-deoxythymidine, azidothymidine, AZT) is a thymidine analogue that, after intracellular phosphorylation, inhibits the replication of the human immunodeficiency virus type 1 (HIV-1), through interference with reverse transcription.^{1,2} Initial clinical studies with zidovudine in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC) showed that it induced clinical and immunological improvements.³⁻⁵ In the spring of 1987 the drug was licensed in many countries for the use in patients with severe HIV-1-related disease.

Zidovudine treatment is associated with toxicities which limit its use.⁶⁻⁹ In this respect bone marrow toxicity is most important. Anaemia, which can be macrocytic or normocytic is frequently found. After prolonged therapy, leukopenia (primarily attributable to neutropenia) and thrombocytopenia can occur. Bone marrow toxicity has been observed more frequently in patients with pretreatment anaemia, neutropenia, low numbers of peripheral blood CD4 positive lymphocytes or a low serum level of vitamin B12.^{6,9} Other toxicities seen in patients receiving zidovudine are headaches, nausea, malaise and myalgia.^{6,13} Myopathy can occur after prolonged treatment.^{10-12,15}

In a recent study from France, during a treatment period of 31 weeks only 21% of patients with AIDS tolerated full-dose treatment without a dose reduction or therapy interruption.⁹ We performed a retrospective analysis with a longer follow-up period (up to 147 weeks) in order to determine the long-term tolerance of zidovudine in our patient population with AIDS and ARC.

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Methods

All patients above 18 years of age from our centre who started zidovudine treatment between May 1987 and July 1988 were studied. Those patients in whom the course of zidovudine therapy was not fully documented were subsequently excluded from analysis. Data on the period between the start of

treatment and the last visit before March 1990, or the time of death were collected from out-patient department records. In most patients the initial dose was 1000 or 1200 mg daily. If there was a need to treat with other myelotoxic therapy, or if there were pre-existing haematological abnormalities, the initial dose was 500 or 600 mg daily.

Data were collected regarding: (a) the duration of zidovudine treatment, (b) dose adjustments, (c) haematological data: haemoglobin, leukocytes and thrombocytes at the start of treatment and at the time of dose adjustment, (d) number of peripheral blood CD4 positive lymphocytes at the start of treatment, (e) concomitant use of other potentially myelotoxic therapy: cotrimoxazole, pyrimethamine, interferon, gangciclovir or cytostatic therapy (local or systemic), (f) CDC classification¹⁴ at the start of treatment.

The following criteria were used to reduce the dose of zidovudine because of myelotoxicity: (a) haemoglobin level below 6.0 g/dl, and/or (b) leukocyte count below $1.5 \cdot 10^9/l$, and/or (c) thrombocyte count below $75 \cdot 10^9/l$.

A change in dosage of zidovudine was considered to be a dose adjustment when a change between the following dose categories was made for a period of more than two weeks: (a) full-dose (> 600 mg/day), (b) reduced dose (≤ 600 mg/day), or (c) interruption of therapy. When patients started with a reduced dose for more than two weeks, this first period also was considered to be a dose adjustment.

The Wilcoxon rank test, the Mann-Whitney U test, and the chi-square test were used for statistical analysis where appropriate.

Results

During a period of 60 weeks a total number of 104 patients from our centre started treatment with zidovudine for AIDS or ARC. All patients were male, the median age was 39 (range: 24–65; mean 40) years. Patients were followed for up to 147 weeks. Seven patients were excluded from this analysis: three because they were treated at other centres during a part of the therapy, and four other patients because records were incomplete. In the remaining 97 patients treatment was started at full-dose in 91 cases. In six cases zidovudine was started in a reduced dose, because of concomitant myelotoxic therapy. During follow-up 70 patients (72%) died.

The median follow-up period for all patients was 67 (range: 3–147; mean 68.3) weeks. For a median of 32 (range: 0–138; mean 38.8) weeks a full dose of zidovudine was used. It was used in reduced dosage for a median of 8 (range: 0–116; mean 17.8) weeks. In 68 patients a total number of 109 dose reductions was observed. Therapy was interrupted for a median of 5 (range: 0–68; mean 11.7) weeks. In 65 patients a total number of 103 therapy interruptions was observed.

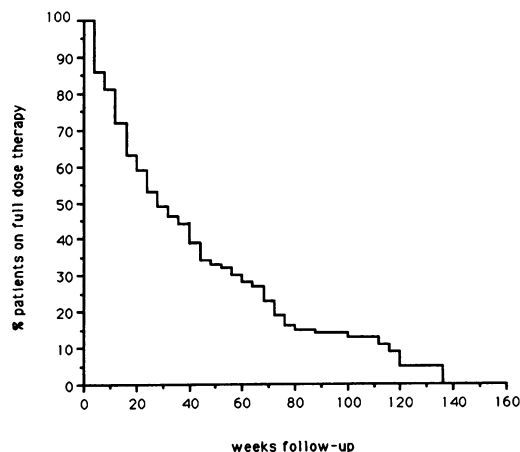


Fig Dose adjustments in full dose therapy because of toxicity or other reasons during 136 weeks follow-up (Kaplan-Meier-curve).

The figure shows the incidence of first dose adjustments in the zidovudine treated patients in time. After one year of treatment the cumulative number of patients with dose adjustments (Kaplan-Meier curve) was 68%, after two years 87%. In those patients who had at least one dose adjustment during their course of therapy, there was a median number of one dose reduction and one therapy interruption.

Table 1 shows the median haematological values at the time of the start of therapy and at the moment of the first dose adjustment. A significant decline in haemoglobin levels and leukocyte counts was observed, while thrombocyte counts did not drop significantly during this period.

Anaemia appeared to be the most common toxicity. In 33 patients (34% of the total population) anaemia was seen at the time of the first dose adjustment. Furthermore, 56 patients (57%) needed one or more blood transfusions during therapy. In this group of patients a median number of five (range: 1–21) transfusions was given. The median number of units of packed red blood cells per patient was 11 (range: 2–72). The median number of transfusions in the total population during zidovudine treatment was

Table 1 Median haematological parameters at the start of treatment and at the time of the first dose adjustment

	Start of treatment	At time of adjustment	
Haemoglobin (g/dl)	7.6 (3.9–10.4)	6.6 (2.2–9.7)	p < 0.001
Leucocyte count ($\cdot 10^9/l$)	3.8 (1.6–13.6)	2.2 (0.6–6.0)	p < 0.001
Platelet count ($\cdot 10^9/l$)	150 (38–335)	135 (8–372)	n.s.

Wilcoxon rank test.
n.s. = not significant.

one (range: 0–21). The median time between the start of therapy and the first blood transfusion was 26 (range: 0–136) weeks. In 20 patients (21%) the first dose adjustment was made because of leukopenia, while thrombocytopenia was reason for a dose adjustment in 10 patients (10%).

Differences in the time of the development of myelotoxicity in distinct cell lines were analysed by comparing the median times from the start of therapy to the moment of first dose adjustment. The median time from the start of therapy to the first dose adjustment was 14 (range: 2–64) weeks in patients ($n = 19$) who had a first dose adjustment because of anaemia without co-existing leukopenia or thrombocytopenia, and 37 (range: 6–85) weeks in patients ($n = 9$) who had a first dose adjustment because of leukopenia without co-existing anaemia or thrombocytopenia ($p = 0.01$, Mann-Whitney U test). In patients with a dose adjustment because of thrombocytopenia ($n = 5$) or myelotoxicity involving more than one cell line ($n = 9$), the median time between the start of treatment and the first dose adjustment was 24 (range: 9–119) weeks. This did not differ significantly from the period found in those who developed solitary anaemia or leukopenia.

The cumulative number of dose adjustments was 212. In 118 cases (56% of all dose adjustments) dose adjustments were made because of haematological abnormalities. Haemoglobin levels were below 6.0 g/dl in 71 cases (33% of all dose adjustments), leukocyte counts below $1.5 \cdot 10^9/l$ in 59 cases (28%) and thrombocyte counts below $75 \cdot 10^9/l$ in 53 cases (25%). In 63 cases (53% of all dose adjustments because of haematological abnormalities) just one cell line was involved. In 55 cases (47%) there was a combination of two or more haematological abnormalities at the time of dose adjustment. There were seven dose adjustments made because of pancytopenia.

Haematological toxicity often recurred in patients who had a dose reduction. When a first adjustment in

the therapy was a dose reduction, this was subsequently followed by therapy interruptions in 40 cases (71% of the patients with a dose reduction). A Kaplan-Meier analysis of all patients with a dose reduction as first dose adjustment in the therapy, showed that 40% were still on zidovudine therapy after 24 weeks, without subsequent stop.

In 59 patients (70%) with dose adjustments concomitant potentially myelotoxic therapy was used, in most cases given in low dosages as secondary prophylactic therapy for opportunistic infections.

In 35 patients (42% of all patients with dose adjustments) no haematological abnormalities were seen. Dose adjustments in these cases commonly were interruptions of therapy because of subjective side effects such as nausea, or because of terminal disease. In only one case clinically evident myopathy, which was histologically proven, was reason for the discontinuation of therapy.

CDC stage of disease, haemoglobin level, and peripheral blood CD4 positive lymphocyte counts at the start of therapy were tested as predictive factors for toxicity. Table 2 shows that CDC classification IV-C1, haemoglobin ≤ 6.0 mmol/l, and CD4 positive lymphocyte counts $\leq 100/mm^3$ were associated with the occurrence of an early dose modification and/or an early blood transfusion. There were no significant differences between groups in the number of patients that eventually developed toxicity.

Discussion

This analysis shows that only a minority of patients with severe symptomatic HIV-1-related disease can tolerate full-dose zidovudine regimens for prolonged periods. After one year of treatment 68% and after two years 87% of the patients had had at least one dose adjustment during their course of therapy (Kaplan-Meier-curve). These findings are comparable with the rate found in the extended follow-up from the original American phase II study.¹⁵

Table 2 Factors predictive for dose adjustment during the course of therapy

Factor	No of patients with dose adjustment: rates (%)	Median time to dose adjustment: weeks (range)	No of patients with blood transfusions: rates (%)	Median time to blood transfusions: weeks (range)
CD4 cells at start of treatment				
≤ 100	54/62 (87%)	17 (0–116)	41/62 (66%)	17 (0–141)
> 100	27/35 (77%)	41 (0–136)	16/35 (46%)	49 (0–132)
	n.s.	$p = 0.01$	n.s.	$p = 0.01$
Clinical stage at start of treatment				
IV-A/C2	9/12 (75%)	25 (0–136)	5/12 (42%)	15 (12–38)
IV-C1	58/64 (91%)	19 (0–77)	43/64 (67%)	18 (0–132)
IV-D	14/17 (82%)	55 (0–116)	8/17 (47%)	50 (0–141)
	n.s.	$p = 0.01$	n.s.	n.s.
unknown: 4 patients				
Hemoglobin at start of treatment				
≤ 6	9/10 (90%)	21 (0–55)	6/10 (67%)	4.5 (0–51)
> 6	74/87 (85%)	22 (0–136)	51/87 (59%)	28 (0–141)
	n.s.	n.s.	n.s.	$p = 0.02$

Differences in time were compared with a Mann-Witney U test, differences in rates were compared with a chi-square test. n.s. = not significant.

Dose reductions and discontinuation of therapy were commonly due to haematological toxicity, as reported previously.^{6,9} Anaemia was the most frequent cause for dose adjustments, followed by leukopenia (which has previously been found to be primarily attributable to neutropenia.⁶ The decline in haemoglobin levels and white blood cell counts from their initial values at the start of treatment until the moment of the first dose adjustment was more pronounced than the decline observed in the thrombocyte count, the latter not reaching a statistical significance. This confirms that the myelotoxic effect of zidovudine especially concerns the red and white cell lines. Thrombocyte counts may even rise during zidovudine therapy.^{6,15-18}

Anaemia was an early sign of toxicity compared to leukopenia. The median time to the development of anaemia was 14 weeks, while leukopenia occurred after a median of 37 weeks of therapy. This difference was significant. Myelotoxicity involving more than one cell line occurred after a median of 24 weeks. This period did not appear to be significantly different from the time to the occurrence of anaemia or from the time to the occurrence of leukopenia. As reported in earlier studies,^{6,9} peripheral blood CD4 positive lymphocyte counts below or equal to 100/mm³, anaemia, and CDC classification IV-C1 at the start of treatment were associated with poor tolerance of full dose zidovudine treatment. Our study, with a longer follow-up, shows that these markers predict a need for an early dose modification or blood transfusion rather than the need for dose modification per se.

Concomitant potential myelotoxic medicine was often used (in 70% of the patients). In most cases it was given as low dose prophylactic therapy for opportunistic infections, which makes it unlikely that this played a major role in the observed toxicity. Although dose reductions were followed by subsequent therapy interruptions in a majority of cases, zidovudine treatment could often be continued for an extended period thereafter; 40% of the patients were still on the drug a half year after a first reduction.

Haematological toxicity was the most common reason for a dose modification. In 35 patients (42% of all dose adjustments) however, zidovudine was stopped for other reasons, such as non-haematological side effects or terminal disease. Myopathy has been reported to occur in an increasing number of patients on long-term zidovudine therapy.^{10-12,15} In this study only one case of histologically proven myopathy was seen, although 54 patients did receive zidovudine for more than a year.

Thus, the majority of patients with AIDS or ARC who are treated with a high dose of zidovudine, at this moment the sole antiretroviral drug which is licensed, cannot be maintained on these regimens, most commonly due to the development of

haematological toxicity. Up until now the established zidovudine starting dose in many countries has been 1000-1500 mg per day. Treatment with lower daily doses of zidovudine may lead to reduced toxicity, while maintaining efficacy.¹³ It is, however, as yet unknown what influence such low-dose regimens will have on the rate at which viral drug resistance develops.¹⁹⁻²¹ Treatment with cytokines, such as granulocyte- and granulocyte-macrophage colony stimulating factors and erythropoietin, may be another promising option to counter zidovudine-induced myelotoxicity.²²⁻²⁴

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