Strategies for Continuing Benefit from Antiretroviral Therapy

Strategies for continuing benefit from antiretroviral therapy were discussed at the Atlanta meeting by Daniel R. Kuritzkes, MD, from the University of Colorado Health Sciences Center in Denver.

Dr Kuritzkes's presentation was largely devoted to a review of clinical trial data on available nucleoside analogues, with some discussion of how such data might affect treatment decisions in patients who have received initial therapy for a given duration and are doing well or who are considered to be failing initial treatment on the basis of virologic, immunologic, or clinical parameters. The discussion generally assumes that initial treatment consists of zidovudine monotherapy. Zidovudine has been found to be superior to other nucleoside analogues in head-to-head comparisons in previously untreated patients and is commonly used as first-line treatment. As noted by Dr Kuritzkes, however, a growing body of data suggests that combination treatment produces greater and more sustained immunologic and virologic effects than does monotherapy. Whether combination therapy will ultimately be considered first-line treatment depends on the results of ongoing study of whether the enhanced response to such therapy is associated with clinical or survival benefits.

Didanosine

In ACTG 116B/117, patients with CD4+ cell counts <300/µL who had received at least 16 weeks of zidovudine monotherapy were randomized to continued zidovudine 600 mg/d or didanosine at dosages of 500 or 750 mg/d. Patients had received an average of approximately 1 year of zidovudine therapy. It was found that: (1) the lower didanosine dosage was associated with fewer new AIDS-defining events or deaths compared with zidovudine treatment; (2) didanosine significantly delayed onset of AIDS or death in patients with AIDS-related complex or asymptomatic disease (Figure 12); (3) survival was equivalent in the three treatment groups; and (4) the duration of prior zidovudine treatment did not alter the benefit of didanosine treatment.

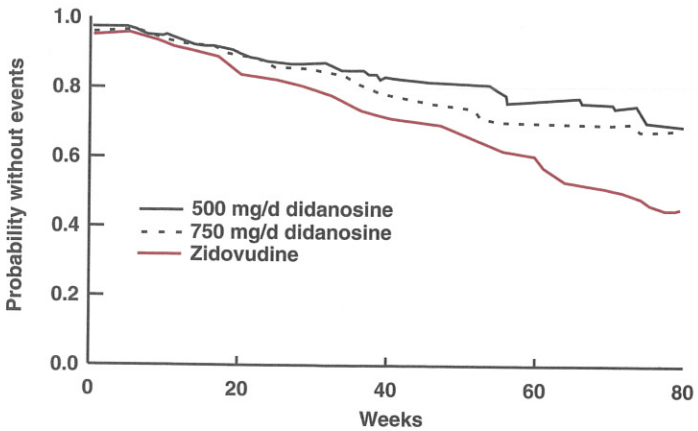

Figure 12. Probability of remaining free of new AIDS-defining event or death for asymptomatic patients or patients with AIDS-related complex among two didanosine dosage groups and continued zidovudine group in ACTG 116B/117. All patients had received ≥ 16 weeks of prior zidovudine treatment. Adapted from Kahn JO et al. *N Engl J Med* 1992.

These findings were confirmed in a subsequent study by Spruance et al in patients progressing (continued decline in CD4+ cell count or recurrence of AIDS-defining illnesses) during zidovudine treatment; in this study, didanosine recipients exhibited delayed progression compared with patients who continued on zidovudine treatment (Figure 13). In another study (ACTG 116A), patients who had received zidovudine for 16 weeks or less received didanosine or continued zidovudine. Zidovudine was superior to didanosine in patients with no prior zidovudine treatment, the treatments were equivalent in patients who had received less than 8 weeks of prior zidovudine, and didanosine treatment was superior in those receiving 8 to 16 weeks of prior zidovudine. As noted by Dr Kuritzkes, the overall data indicate that patients who have been receiving zidovudine treatment may benefit from a change to didanosine treatment but do not provide guidelines for when such a switch should be made. Based on the hypothesis that the benefit of didanosine, which does not exhibit cross-resistance with zidovudine, was associated with the presence of zidovudine resistance, a virology study involving a subset of ACTG 116B/117 patients was performed to assess the impact of phenotypic and genotypic zidovudine resistance on treatment outcome. It was found that patients harboring virus with phenotypic resistance or zidovudine resistance mutations were more likely to progress irrespective of the treatment they received and that the benefit of switching to didanosine could not be accounted for solely on the basis of zidovudine resistance. According to Dr Kuritzkes, one conclusion of this study is that monitoring for zidovudine resistance may not be helpful for determining when alteration of treatment should occur.

The most common serious adverse event in patients taking didanosine is pancreatitis. The incidence of this adverse effect has ranged from 2.5% to 8% in different patient series. Approximately 6% of cases have been fatal, with the overall rate of fatality due to pancreatitis being approximately 0.3% in all treated patients.

Zalcitabine

In ACTG 114, zalcitabine was compared with zidovudine in previously untreated patients with CD4+ lymphocyte counts of less than 300/µL. It was found that zidovudine treatment was associated with a lower risk of clinical disease progression and increased survival. In CPRCA 002, patients who were either intolerant of or who had failed zidovudine treatment were given either didanosine or zalcitabine. The patients had very advanced disease, as indicated by the median CD4+ cell count of 37/µL. No significant difference between treatments was observed with regard to disease progression or death. According to Dr Kuritzkes, although the conclusion of the study was that the two agents were

of equivalent efficacy in the patient population, it is possible that, given the advanced illness of the study patients, drug therapy was of little benefit in many patients. Two thirds of patients experienced adverse events. Peripheral neuropathy, the primary toxicity of zalcitabine, was significantly more frequent among zalcitabine recipients, whereas gastrointestinal events were more common in didanosine patients. Stomatitis occurred only in zalcitabine recipients and pancreatitis occurred only in didanosine recipients.

Stavudine

Stavudine has been granted provisional approval by the FDA on the basis of analysis of CD4+ cell count and p24 antigen responses in a study sponsored by Bristol-Myers Squibb (BMS 019) comparing stavudine with continued zidovudine in patients with 50 to 500 CD4+ cells/μL and less than 6 months of prior zidovudine therapy. Initial analysis showed that stavudine treatment was associated with a significant increase in CD4+ cell count and decreases in viral load as measured by p24 antigen levels and viral titers in PBMCs, with patients who continued on zidovudine exhibiting a progressive decline in CD4+ count. The differences in CD4+ cell counts and HIV viral load between the two treatments remained significant after 48 weeks of follow up. Subjects who received stavudine had a longer time to a protocol-defined treatment failure than subjects who received zidovudine ($P = 0.002$). Progression to AIDS and death also favored stavudine ($P = 0.007$); subjects who received stavudine had a longer survival time, but the difference was not significant ($P = 0.07$).

The primary toxicity of stavudine is peripheral neuropathy. In BMS 019, approximately 20% of patients exhibited some symptoms of peripheral neuropathy over 24 months of follow up. Another open-label study indicates that the incidence of neuropathy is dose-related. A low dose of stavudine is currently recommended for compassionate use. Study of a higher dose of stavudine continues, and the ultimate optimum dosage recommendations for this drug remains to be determined.

Combination Therapy

As stated by Dr Kuritzkes, there are a number of compelling reasons to add another agent to zidovudine treatment in patients who have clinical disease progression on zidovudine or who have received monotherapy for extended periods of time, to begin treatment with combination therapy. These reasons include the potential for additive or synergistic antiviral effects, prevention of emergence of resistance, and potentiation of the anti-HIV effect by attacking the virus at different stages of its life cycle. In vitro additive or synergistic effects in vitro have been observed for many combinations of antiretroviral agents against a number of HIV strains and including zidovudine-resistant virus. As noted by Dr Kuritzkes, the potential for limiting emergence of resistance has long held theoretical appeal but has been difficult to demonstrate. He stated that evidence of such an effect is beginning to emerge, particularly in the context of combination treatment with zidovudine and lamivudine (3TC). The potential for attacking the virus at different stages of its life cycle has begun to be realized with the advent of protease inhibitors as a potential combination treatment option.

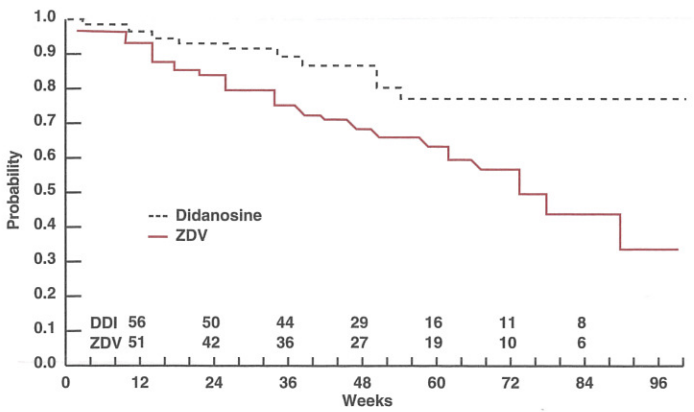

Figure 13. Probability of clinical progression among patients who received either didanosine (ddI) or continued zidovudine (ZDV) after exhibiting clinical or immunologic progression on zidovudine monotherapy. Adapted from Spruance, et al. *Ann Intern Med* 1994.

Potential problems with combination therapy include overlapping toxicity, such adverse interactions as antiretroviral antagonism or pharmacokinetic opposition, difficulty with adherence, and cost. With regard to overlapping toxicity, Dr Kuritzkes stated that it may be unadvisable to combine stavudine and zalcitabine given the shared adverse effect of peripheral neuropathy. There are conflicting data concerning the potential antagonism of stavudine and zidovudine via competition for phosphorylation by intracellular kinases. To address this question, the combination is being tested in two ACTG trials.

Available data support the use of concomitant rather than alternating combination therapy, although a number of studies comparing the effects of the strategies continue. In a pilot study performed by Yarchoan and colleagues, patients received either zidovudine 300 mg/d plus didanosine 250 mg/d or alternating 3 week courses of zidovudine 600 mg/d and didanosine 500 mg/d. Mean changes in CD4+ cell counts in the concomitant and alternating treatment groups were +66/μL and +20/μL, respectively, at 18 weeks, +68/μL and +4/μL, respectively, at 27 weeks, and +75/μL and -12/μL, respectively at 54 weeks.

According to Dr Kuritzkes, there are now data from a number of small trials indicating superiority of combination therapy over monotherapy. In ACTG 106, patients receiving various dosages of zidovudine and zalcitabine in combination had significantly greater and more prolonged increases in CD4+ cell count than those receiving zidovudine monotherapy, although the monotherapeutic zidovudine dosage was much lower (ie, 150 md/d) than that currently used. In ACTG 143, symptomatic patients received didanosine alone or one of three zidovudine-didanosine combinations. Although increases in CD4+ cell count were similar among treatment groups, combination therapy patients exhibited a significantly greater reduction in viral load.

Similar results were observed in a pilot study of zidovudine plus zalcitabine. In a study comparing zidovudine monotherapy with zidovudine plus either zalcitabine or didanosine in patients with less than 300/μL CD4+ cells and less than 4 weeks of prior zidovudine, combination therapy patients had significantly greater increases in CD4+ cell count and reductions in viral load, as measured by plasma HIV RNA levels. Improvements in these

measures persisted for more than 1 year in the combination therapy group compared with 24 weeks in the zidovudine monotherapy group.

Currently, there are data available from only one trial of combination therapy that included clinical end points. In ACTG 155, symptomatic patients with a CD4+ lymphocyte count ≤300/μL and asymptomatic patients with a count of ≤200/μL who had received at least 6 months of prior zidovudine received continued zidovudine, zalcitabine, or the combination of the two. The study as a whole did not show a benefit of combination therapy over monotherapy with regard to survival or disease progression. However, trend analysis showed a significant benefit of combination therapy compared with zidovudine monotherapy as pretreatment CD4+ cell count increased. In particular, it was found that combination therapy was associated with an improvement in clinical outcome compared with zidovudine monotherapy among patients with initial CD4+ cell counts ≥150/μL; combination treatment was also associated with a more sustained improvements in CD4+ cell count in this subpopulation. Severe toxicities were less common in patients with higher CD4+ cell counts.

As related by Dr Kuritzkes, the treatment protocol in this study mandated that study medication be withdrawn in cases of toxicity, and toxicity was more common among combination therapy recipients who had both drugs withdrawn in cases of toxicity. Thus, particularly among patients with lower CD4+ cell counts, combination therapy patients received less cumulative drug therapy than did monotherapy patients, a factor that could at least in part account for the finding of no greater benefit of combination treatment in the lower CD4+ cell strata. Treatment protocols in subsequent, combination therapy studies have been designed to permit greater flexibility and discretion of clinical investigators in responding to toxicity, including the latitude to hold or discontinue only the drug believed to be responsible for the observed toxicity in a patient receiving combination treatment. Better information on toxicity management in the context of combination treatment can be expected from such studies. According to Dr Kuritzkes, a second large trial of combination therapy as either initial or subsequent treatment in patients with CD4+ cell counts of 200-500/μL (ACTG 175) is nearing completion.

Lamivudine

Dr Kuritzkes briefly reviewed some of the findings from trials with lamivudine (3TC), which is currently available from the manufacturer through an expanded access program. Rapid emergence of high-level resistance to lamivudine, associated with a mutation at codon 184 of the reverse transcriptase dampened the initial enthusiasm for this drug. However, it was subsequently found that although codon 184 mutants emerged within 4 weeks of treatment with lamivudine monotherapy, viral load remained at or below 50% of baseline values, suggesting a persistent antiviral effect despite the development of resistance. Other findings suggest the effectiveness of lamivudine-zidovudine combination treatment.

In two European studies assessing the combination of lamivudine-zidovudine, one in zidovudine-naive patients (NUCB 3001) and one in zidovudine-experienced patients (NUCB 3002), combination treatment resulted in significantly greater and more sustained elevations in CD4+ cell counts than did zidovudine monotherapy, with changes in viral load markers mirroring the CD4+ cell count responses. The emergence of zidovudine-resistant isolates appeared to be markedly delayed in patients receiving the combination regimen.

Potential Strategies

Dr Kuritzkes outlined potential strategies for continuing antiretroviral therapy in patients initially receiving zidovudine monotherapy. He indicated that alternative monotherapy might particularly be considered an option in asymptomatic patients with declining CD4+ cell counts that remain above 300/μL or who have been on zidovudine monotherapy for some time. In such cases, he suggested that didanosine or stavudine might be substituted for zidovudine. He indicated that lamivudine cannot yet be considered a rational choice for alternative monotherapy apart from its use in patients intolerant of the other nucleoside agents, given the concern about rapid emergence of resistance. He stated that although the available data indicate that lamivudine and zidovudine have roughly equivalent effects on viral load in zidovudine-naive patients when used as monotherapy, he would probably use stavudine or didanosine, as alternative monotherapy because of the data suggesting their clinical benefit, until further information on lamivudine becomes available.

Although alternative monotherapy is an option, it is his practice to add didanosine or zalcitabine to zidovudine in patients who appear to be progressing or who have been on zidovudine for some time. He suggested that zalcitabine may be better tolerated than didanosine in terms of compliance, given the problems with the palatability of the latter. Data comparing different combination regimes with monotherapy in terms of clinical outcome differences are expected from the analyses of ACTG 175 and CPCRA 007. The combination of zidovudine and stavudine is also being evaluated in a clinical trial, which should answer questions about antiretroviral antagonism. Lamivudine currently is available for use in patients progressing on zidovudine who have CD4+ cell counts less than 300/μL. As related by Dr Kuritzkes, the lamivudine compassionate-use program does not require that other antiretroviral treatment be discontinued. He predicted that, in light of the data suggesting a benefit of the lamivudine-zidovudine combination, many practitioners may begin to use this combination.

Finally, Dr Kuritzkes mentioned that a study in symptomatic pediatric patients comparing zidovudine, didanosine, and the combination of the two has been partly terminated. Although the trial is still partly blinded and analysis of the findings will not be completed until August 1995, it appears that the outcome in the zidovudine monotherapy arm was inferior to that in one of the other treatment arms, most likely the combination arm. Dr Kuritzkes stated that the final data from this trial may significantly influence thinking on whether therapy should begin with monotherapy or combination therapy.

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