Safety, efficacy and pharmacokinetics of linezolid for treatment of resistant Gram-positive infections in cancer patients with neutropenia

P. F. Smith1,2, M. C. Birmingham2, G. A. Noskin1, A. K. Meagher2, A. Forrest2, C. R. Rayner4 & J. J. Schentag2

1Roswell Park Cancer Institute, Buffalo, NY; 2Clinical Pharmacokinetics Laboratory, State University of New York at Buffalo, NY; 3Northwestern University Medical School, Chicago, IL, USA; 4Department of Pharmacy Practice, Monash University, Parkville, Australia

Received 24 May 2002; revised 21 November 2002; accepted 21 November 2002

Background: Linezolid is a recently approved oxazolidinone with extended activity against Gram-positive bacteria. We evaluated the results of linezolid therapy in neutropenic cancer patients with Gram-positive bacterial infections from a compassionate-use program.

Patients and methods: This was a prospective, multicenter, open-label, non-comparative, non-randomized compassionate-use treatment program in patients with serious Gram-positive infections. To qualify for enrollment patients were required to have an infection resistant to available antimicrobial agents, or in whom available agents had failed or to which they were intolerant. Patients with absolute neutrophil counts (ANC) <500 cells/mm3 or <1000 cells/mm3 and expected to decrease to <500 cells/mm3, and who received linezolid 600 mg twice daily were included. Plasma samples for population pharmacokinetic analysis were collected. Clinical and microbiological assessments of outcomes were made at the end of therapy and at short-term follow-up.

Results: Of the patients in the compassionate-use trial, 103 were neutropenic. The mean (standard deviation (SD)) age was 50.1 (17.5) years, 47% were female, and 47.6% had a baseline ANC ≤100 cells/mm3. The mean (SD) duration of linezolid therapy was 14.6 (11.4) days. The most common site of infection was the bloodstream (90.3%), and the most commonly identified pathogen was vancomycin-resistant Enterococcus faecium (83%). A total of 83 (80.5%) and 52 (50.4%) patients were evaluable for clinical and microbiological outcomes at the end of therapy, respectively. Clinical and microbiological cure rates in the evaluable patients were 79% and 86%, respectively. Linezolid was well-tolerated in this patient population, with an overall adverse event rate of 17.5%; 5% of patients required discontinuation of the drug due to side-effects. The pharmacokinetics of linezolid in patients with neutropenia did not differ from the overall compassionate-use population.

Conclusions: Linezolid was safe and effective in treating resistant Gram-positive infections in neutropenic cancer patients. Comparative clinical trials to evaluate further the effectiveness and safety of linezolid in this patient population are warranted.

Key words: cancer, linezolid, neutropenia, resistance

Introduction

With the introduction of potent immunosuppressive therapies and cytotoxic chemotherapeutic agents, the number of patients at risk for complications of neutropenia continues to grow [1, 2]. Infection remains the leading cause of death in cancer patients with neutropenia, and appropriate antibiotic therapy can significantly reduce mortality. As the epidemiology of infection in the cancer patient evolves, the prevalence of Gram-positive bacteria, especially multidrug-resistant strains, has become increasingly common. Patients who become neutropenic following the administration of cytotoxic chemotherapy are at particular risk for the morbidity and mortality associated with such difficult-to-treat infections [3–7].

This increasing prevalence of multidrug-resistant Gram-positive bacterial infections has prompted the development of new antimicrobials with expanded activity against organisms resistant to agents such as penicillin, methicillin (oxacillin) and vancomycin. A new class of synthetic antimicrobials with extended Gram-positive activity, the oxazolidinones, has recently been developed. Oxazolidinones provide activity against penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci [8–17]. This class of compounds possesses a unique mechanism of action, binding to the bacterial 50S ribosomal subunit to inhibit the
initiation of protein synthesis [18]. Because of this unique mechanism, oxazolidinones do not demonstrate cross-resistance with currently available antibiotics.

Linezolid is the first member of the oxazolidinone class to be approved for use in the United States. Published reports have demonstrated its effectiveness for a variety of infections in immunocompetent individuals [19–22]. Linezolid is administered either intravenously or orally, with a bioavailability of 100% and a half-life of 5–7 h, providing for twice-daily dosing [23, 24]. Before US Food and Drug Administration approval, linezolid was made available through a compassionate-use program for patients with serious Gram-positive bacterial infections without adequate alternative treatment options. Results from patients treated under this program have been previously described, and demonstrated the efficacy and safety of linezolid in treating Gram-positive infections [25]. The purpose of this report was to analyze the safety, effectiveness and pharmacokinetics of linezolid in the subset of patients with neutropenia treated under this compassionate-use program.

**Patients and methods**

**Study design**

This was a prospective, multicenter, open-label, non-comparative, non-randomized compassionate-use treatment program. The purpose of the program was to provide linezolid to patients with serious infections due to Gram-positive organisms resistant to available agents, or for patients intolerant of or in whom conventional therapy had failed. Enrollment into the trial required microbiological documentation of an active infection, with clinical signs and symptoms consistent with an infection [26]. Entry criteria required the organism to be resistant to appropriate marketed antimicrobials, or the patient to be intolerant of acceptable therapy. Patients were excluded if they had known hypersensitivity to oxazolidinones, or if they satisfied inclusion/exclusion criteria for enrollment in another linezolid study at an active study site. In addition to the enrollment criteria for the compassionate-use program, the current analysis required cancer patients to be neutropenic at baseline, defined as an absolute neutrophil count (ANC) <500 cells/mm³, or <1000 cells/mm³ and decreasing to <500 cells/mm³ during therapy.

From October 1997 to May 2000, 796 patients (828 treatment courses) were enrolled in the overall compassionate-use program. Of the 805 treatment courses in adults, the median (range) age was 55.8 (18–93) years. Five hundred and fifty-six treatment courses (67.1%) were ≤28 days (mean 14.0) and the remaining 272 treatment courses (32.9%) were >28 days (mean 53.8). Oral therapy was used at some point in the treatment course for 46.1% of patients, and 21.7% were treated solely with oral linezolid. Clinical and microbiological response rates for the overall compassionate-use population in the evaluable patient population was 91.5% and 85.8%, respectively. For the intention-to-treat analysis of the overall compassionate-use population, clinical and microbiological cure rates were reported as 73.3% and 82.4%, respectively [25].

**Study procedures**

Written informed consent was obtained for each patient before enrollment, and the study protocol was approved by each local institutional review board. Patients received linezolid 600 mg intravenously or orally twice daily, and dosage adjustment was not required for either renal or hepatic dysfunction. Treatment duration ranged from 5 to 28 days, depending on site of infection, and up to 3 months of therapy was allowed with prior approval. Because of potential monoamine oxidase inhibition by linezolid [9], patients were screened and monitored for potential interacting medications, but the medications were not routinely discontinued if they were either medically necessary (i.e. vasopressors), or would have required a long duration to be completely eliminated before the initiation of linezolid therapy (i.e. serotonin-specific reuptake inhibitors).

Baseline peripheral blood cultures, cultures of the suspected infection site, laboratory tests and physical examination were obtained within 24 h before starting linezolid. The antimicrobial activity of the baseline isolates to linezolid was tested at the institution’s local laboratory, and the majority of the isolates were sent to a central microbiology laboratory (Covance, Indianapolis, IN, USA) for additional evaluation. Routine laboratory tests included hematology, serum chemistry, liver function tests, urinalysis and pregnancy tests for females of child-bearing potential. Follow-up cultures were obtained every 48 h for 6 days, or until cultures became negative. Laboratory tests for safety were performed every 3 days for the first 21 days of treatment, and weekly thereafter until the end of therapy. Patients received daily clinical evaluations while receiving intravenous therapy, and every 3 days while on oral therapy. After 21 days of therapy, clinical assessments were performed weekly until linezolid treatment was completed.

**Evaluation of outcomes**

The clinical outcome for each patient was determined by the site investigator. Clinical response was categorized as cure (resolution of signs and symptoms of disease), failure (persistence of presenting signs or symptoms and/or new unfavorable findings relating to clinical efficacy measures by infection site), or indeterminate (extenuating circumstances preclude classification). Clinical response rates were computed as the number of patients in the cured category divided by the total number of patients. An intention-to-treat analysis was similarly performed in which all patients receiving at least one dose of study drug were included. Patients with indeterminate outcomes were excluded from the evaluable population, and treated as failures in the intention-to-treat population. The test of cure for this analysis was defined as the treatment outcome at the end of therapy.

Microbiological outcomes were classified as eradication, presumed eradication, persistence, eradication with reinfection, or indeterminate response. Presumed eradication was utilized in cases where clinical cure was achieved and the infection site precluded follow-up cultures at the end of therapy. Microbiological response rate was defined as the number of patients with eradication or presumed eradication divided by the total number of patients in the analysis. An intention-to-treat analysis was also performed for microbiological outcomes.

**Adverse events**

Both laboratory and clinical adverse events were evaluated prospectively by each investigator throughout the treatment and post-treatment periods. The causality of the adverse events (both serious and non-serious) to linezolid was determined by the site investigator as being either probably, possibly, or unlikely to be related to study drug. Adverse events that were classified as either probably or possibly related to linezolid were combined for this analysis. Adverse events requiring discontinuation of study drug were also recorded.

**Pharmacokinetics**

Plasma samples were collected for quantification of linezolid concentrations. After harvesting plasma by centrifugation, samples were frozen and shipped on dry ice to a central laboratory and assayed by a validated high performance liquid chromatography assay with ultraviolet detection. The assay has a lower limit of quantification of 0.01 mg/l, and an interday coefficient of variation (CV) <7% [27]. Population pharmacokinetic procedures as previously reported were used to analyze the plasma concentration data [28]. In summary, the pharmaco-
The maximum velocity of capacity limited clearance (\(= \frac{V_{\text{max}}}{K_{\text{m}} + C}\)) of linezolid was 1.5 mg/l (range 0.5–4). The pharmacokinetic results from normal volunteers were utilized as initial Bayesian priors [31]. The following pharmacokinetic parameters were fitted or derived using data from each subject: volume of distribution of the central and peripheral compartments, volume of distribution at steady state, distributional clearance, ratio of drug cleared by the linear pathway divided by the estimated creatinine clearance, the Michaelis–Menten constant \(K_{\text{m}}\), intrinsic clearance \(CL_i\), and the maximum velocity of capacity limited clearance \(= \frac{V_{\text{max}}}{K_{\text{m}} \times CL}\). Area under the concentration–time curve (AUC) was determined by numeric integration of the fitted model. Because none of the neutropenic patients received oral linezolid, bioavailability could not be assessed in this patient population. The pharmacokinetics of linezolid in patients with neutropenia was compared with the overall compassionate-use population.

Statistical analysis
Differences in clinical outcomes and pharmacokinetic parameters were evaluated using non-parametric methods, \(\chi^2\) or the Kruskal–Wallis one-way analysis of variance or the Mann–Whitney test in cases involving two independent groups. All statistical tests were computed in SYSTAT (Version 10; SPSS, Inc., Chicago, IL, USA). A \(P\) value <0.05 was required for a declaration of statistical significance.

Results

Demographic characteristics
Between October 1997 and May 2000, 796 patients were enrolled in the compassionate-use program at 278 sites in the United States. Of these, 103 patients with neutropenia were included, with demographic characteristics summarized in Table 1. The majority of patients enrolled were adults; however, five pediatric patients, ranging from 1.6 to 12 years were also included. All of these patients were hospitalized during treatment. The majority (88 of 103) were undergoing therapy for hematological malignancies, including 33 who had received hematopoietic stem cell transplantation. The most commonly identified pathogen was vancomycin-resistant enterococci (Table 2). The mean baseline linezolid minimum inhibitory concentration (MIC) for all Gram-positive bacteria was 1.5 mg/l (range 0.5–4). There was no microbiological evidence of antimicrobial resistance to linezolid in this patient population.

The most common site of infection was the bloodstream (93 of 103 cases, 90.3%), with 44% of these associated with a central venous access device. There were three patients each with skin and skin structure and urinary tract infections, and two patients each with endocarditis and osteomyelitis. The mean [standard deviation (SD)] treatment duration for all patients was 14.6 (11.4) days, and ranged from 1 to 69 days. Patients with ANC <100/mm\(^3\) at the time of study entry received linezolid therapy for an average of 17 days, which was not significantly different from patients with higher baseline values (\(P = 0.20\)).

Clinical and microbiological outcomes
Of the 103 patients enrolled, 77 were evaluable for clinical outcome, and 52 for microbiological outcome. The majority of patients who were not evaluable received <5 days of therapy, the majority died before the fifth day. The overall mortality rate, at the completion of all study follow-up visits, for all neutropenic patients enrolled in the compassionate-use program was 33% (34 of 103).

Clinical and microbiological response rates for the evaluable population were 79% and 86%, respectively (Figure 1). For the
intention-to-treat analysis, the response rates were 57% for clinical outcomes, and 45% for microbiological outcomes. Evaluable patients with ANCs <100 cells/mm<sup>3</sup> tended to have a lower clinical response rate, 69% compared with 86% for patients with a baseline ANC >100 cells/mm<sup>3</sup>. However, this difference did not meet statistical significance (P = 0.07). For the intention-to-treat population, the overall clinical response rate was 55% in patients with a baseline ANC <100 cells/mm<sup>3</sup>, and 59% for those >100 cells/mm<sup>3</sup> (P = 0.70).

Five patients were enrolled with vancomycin allergies, and 18 patients were treated following either intolerance or clinical failure of quinupristin/dalfopristin. Intolerance requiring quinupristin/dalfopristin discontinuation occurred in nine patients, due to myalgias/arthritis (seven patients), elevated bilirubin concentrations (three patients) and rash (two patients). Three of these patients suffered both myalgias/arthritis and elevated bilirubin concentrations. Eight patients failed to improve while receiving quinupristin/dalfopristin therapy, and one additional patient had Enterococcus faecium reported to be intermediately susceptible to this agent. Of the eight patients switched to linezolid therapy for failure to improve on quinupristin/dalfopristin, three were successfully cured.

Safety

The overall adverse event rate in this population was 17.5%, and two patients had multiple events (Table 3). The most common side-effects were increased liver function tests (n = 5), rash (n = 5) and gastrointestinal disturbances (n = 4). Three patients required discontinuation of therapy for rash, one for elevated liver function tests and one for thrombocytopenia. Overall, linezolid treatment was well-tolerated in 85% of all patients, with ~7% having some tolerability problems not requiring discontinuation, and 5% requiring discontinuation of therapy due to side-effects. No clinical evidence of monoamine oxidase inhibition was observed, even in patients treated with potentially interacting medications.
Table 4. Mean pharmacokinetic parameters (percent coefficients of variation) of linezolid in patients with neutropenia compared with the complete compassionate-use patient population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neutropenia (n = 56)</th>
<th>All patients (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state volume of distribution (l/65 kg)</td>
<td>62.2 (20)</td>
<td>64.6 (38)</td>
</tr>
<tr>
<td>Intrinsic clearance (l/h/65 kg)</td>
<td>44.0 (48)</td>
<td>39.7 (93)</td>
</tr>
<tr>
<td>Michaelis–Menten constant (µg/ml)</td>
<td>1.35 (34)</td>
<td>1.30 (112)</td>
</tr>
<tr>
<td>Maximum velocity of capacity-limited clearance (mg/h/65 kg)</td>
<td>52.9 (21)</td>
<td>51.8 (45)</td>
</tr>
<tr>
<td>Total clearance (l/h/65 kg)</td>
<td>8.3 (60)</td>
<td>6.7 (48)</td>
</tr>
<tr>
<td>24-hour area under the concentration–time curve (µg·24 h/ml)</td>
<td>211.7 (49)</td>
<td>191 (58)</td>
</tr>
</tbody>
</table>

*P >0.05 for all comparisons.*

collected per patient ranged from two to eight, with a median of four samples collected per patient. The pharmacokinetic model fit the data well, with an overall mean r² = 0.98. The mean (CV%) 24-h AUC was 212 (49) µg·24 h/ml, the mean (CV%) 24-h AUC/MIC ratio was 132 (65) per serum inhibitory titre, and ranged from 19 to 433. The mean (CV%) percent of the dose interval that drug concentrations remained above the MIC was 90.5% (16.3), and ranged from 31.5% to 100%. Pharmacokinetic parameters in the neutropenic population did not differ significantly from the overall compassionate-use population (*P >0.05*).

**Discussion**

Linezolid was well-tolerated and efficacious in treating this group of 103 neutropenic patients with documented Gram-positive infections and few alternative treatment options. Patients with severe neutropenia (ANCs <100 cells/mm³) tended to have lower response rates than those with higher baseline neutrophil counts, although this difference did not reach statistical significance.

As expected, the neutropenic population was more difficult to treat than the overall compassionate-use population, with lower clinical cure rates (79% versus 92% in the evaluable patients). The clinical cure rates with quinupristin/dalfopristin in patients with neutropenia have also been reported. Raad et al. [32] reported a clinical response rate of 68% in 56 immunocompromised cancer patients, while the cure rate in 14 evaluable patients from the quinupristin/dalfopristin emergency-use protocol was 64.3% [33]. These patients were limited to those with vancomycin-resistant *Enterococcus faecium* infections.

Because the incidence of vancomycin- and methicillin-resistant Gram-positive infections in immunocompromised hosts continues to increase, alternative options for treatment are necessary. Currently available antimicrobial agents such as linezolid and quinupristin/dalfopristin provide new options to treat such patients. Unfortunately, experience with these drugs in patients with neutropenia is limited. This is the first report summarizing the experience of linezolid in this patient population from the compassionate-use program. Based on the results, linezolid appears to be an effective antimicrobial agent for previously difficult-to-treat pathogens.

It should be noted that the majority of these patients were infected with vancomycin-resistant enterococci, most frequently of the bloodstream. While enterococci are not particularly pathogenic organisms, they have been clearly shown to result in significant morbidity and mortality [34–36]. Further study and clinical experience is needed to evaluate more thoroughly linezolid use in such infections involving immunocompromised hosts.

Linezolid has demonstrated excellent activity against a broad range of Gram-positive bacterial pathogens. This extended activity should make it less likely for patients treated with linezolid to experience superinfection with other Gram-positive organisms during therapy, and superinfection was not observed in this patient population. This is in contrast to alternatives such as quinupristin/dalfopristin, which lacks activity against organisms such as *Enterococcus faecalis*. Superinfection with Gram-positive bacteria has been reported in patients undergoing quinupristin/dalfopristin therapy [33].

The pharmacokinetics of linezolid in patients with neutropenia was also evaluated in this report. This is of particular importance for immunocompromised hosts, to ensure that adequate drug concentrations are achieved. The pharmacokinetics of linezolid in these patients did not differ from the overall compassionate-use population. Therefore, dose adjustments for neutropenia are not necessary for pharmacokinetic reasons, with equivalent dosages resulting in equivalent drug concentrations, regardless of neutrophil counts.

It has been shown that the time to neutrophil recovery is an important aspect of caring for patients with neutropenia [37]. When a new drug is used in this population, it should be evaluated for a potential impact on the neutrophil recovery process. This is also relevant to linezolid, as long-term treatment has been associated with the potential to cause reversible myelosuppression [38–41]. This effect has not been well characterized in this patient population; however, the incidence appears to be low, and the onset delayed [42, 43]. The average duration of treatment in this study was ∼14 days, and may not be of sufficient duration to appreciate fully such an effect. The heterogeneous population and lack of information available regarding prior myelosuppressive chemotherapy and use of colony-stimulating factors precluded a formal evaluation. However, the majority of patients in this population did recover from neutropenia, and there was no obvious trend that would suggest time to recovery was blunted. Similarly, the effect of linezolid on platelet counts could not be readily assessed, and should be considered carefully in this patient population, as linezolid has been associated with thrombocytopenia when administered for >2 weeks [42, 43]. In the current study, two patients were diagnosed with thrombocytopenia, one requiring discontinuation. Continued vigilant post-marketing surveillance or a randomized comparative trial in a homogeneous population would be needed to evaluate fully the potential effect of linezolid on hematological indices.
An important limitation of this study is its non-comparative, unblinded design. However, based on these results from the compassionate-use program, it appears that linezolid is an effective agent in the treatment of infections in neutropenic patients that are caused by resistant Gram-positive organisms, primarily vancomycin-resistant enterococci. The microbiological results, a more objective measure of an antimicrobial agent’s effectiveness, illustrated that linezolid was effective in eradicating the causative organisms in these immunocompromised patients. Future clinical trials to evaluate the effectiveness and safety of linezolid in this patient population are warranted.

Acknowledgements

The authors are indebted to the compassionate-use patients, investigators, and study coordinators. This program would not have been possible without considerable efforts by the following clinical pharmacists who contributed to the screening and enrollment process: G. S. Zimmer, J. D. Root, K. E. Welch, P. A. Moise, J. D. Scott, K. K. Gilliland, L. D. Dresser, T. R. Perry, A. M. O’Donnell and research assistants S. Flavin and V. Ma. The linezolid compassionate-use program was supported by the Pharmacia Corporation.

References


