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Combination Effect of Recombinant Human Interleukin-1α with Antimicrobial Agents

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Combination effects of recombinant human interleukin-1α with ceftazidime, moxalactam, gentamicin, enoxacin, amphotericin B, miconazole, or an immunoglobulin preparation were evaluated in systemic infections with *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Candida albicans* in normal mice and systemic infection with *P. aeruginosa* in mice with leukopenia induced by preadministration of cyclophosphamide. Synergistic effects were generally observed at interleukin-1α doses as low as 1 to 30 ng per mouse with most combinations. The results show the possibility that recombinant human interleukin-1α could be of help for treating obstinate infections not successfully treated with antimicrobial agents alone.

Although many microbial infections are usually treated successfully with antimicrobial agents, some infections are still difficult to cure by antimicrobial agents alone; i.e. pseudomonal infections, fungal infections, infections in immunocompromised hosts, etc. The efficacy of chemotherapy depends on not only the antimicrobial and pharmacological properties of the agents used but also the host defense abilities of the patients. Interleukin-1 (IL-1) is a cytokine produced by a variety of host cells upon infection, inflammation, and immunological stimuli; and it mediates pleiotropic host responses (3, 4). We found previously that recombinant human IL-1α (rHu IL-1α) augmented host resistance to microbial infections caused by various microorganisms in mice (10, 18), and such augmentation has been confirmed by other groups (9, 23). rHu IL-1β has similar activity (22, 23). These findings suggest that combination therapy of IL-1 with antimicrobial agents might be useful for controlling obstinate infections. In this study, we examined combination effects of rHu IL-1α with various chemotherapeutic drugs in experimental infections in mice.

MATERIALS AND METHODS

Materials. rHu IL-1α was produced in our laboratories, and its properties were described previously (15). Ceftazidime sodium was purchased from Glaxo Japan Co., Ltd., Tokyo, Japan; moxalactam sodium and cyclophosphamide were from Shionogi & Co., Ltd., Osaka, Japan; gentamicin sulfate was from Essex Nippon Co., Ltd., Osaka, Japan; enoxacin and a pooled immunoglobulin preparation were from Dainippon Pharmaceutical Co., Ltd., Osaka, Japan; amphotericin B was from Squibb Japan Inc., Tokyo, Japan; and miconazole nitrate was from Sigma Chemical Co., St. Louis, Mo.

Assessment of combination effect. The combination effects of rHu IL-1α and antimicrobial agents were assessed in experimental infection models in mice. Infection was induced by inoculating eight male Std-ddY mice weighing approximately 25 g intraperitoneally with 1×10^7 CFU of *Pseudomonas aeruginosa* 12 per mouse, intravenously with 4×10^7 CFU of *Candida albicans* 3170 per mouse, or intraperitoneally with 2×10^2 CFU of *Klebsiella pneumoniae* P-5709 per mouse. Inocula were prepared by diluting *P. aeruginosa* and *K. pneumoniae* cultures in Trypto Soy broth (Eiken Co., Tokyo, Japan) with the same broth and by suspending *C. albicans* precultured on Sabouraud agar (Difco Laboratories, Detroit, Mich.) in physiological saline and then diluting with the same menstruum. Leukopenic mice were produced by intraperitoneally injecting female Jcl-ICR mice weighing about 25 g with cyclophosphamide at a dose of 300 mg/kg (body weight) 4 days before bacterial inoculation. Infection in leukopenic mice was induced by inoculating groups of eight mice intraperitoneally with 5×10^2 CFU of *P. aeruginosa* 12 per mouse. rHu IL-1α was intramuscularly injected 3 days and 1 day before infection except for the *K. pneumoniae* infection, for which it was injected immediately after infection and 1 day later. These dose timings are proper for rHu IL-1α to augment host resistance to these infections, as described previously (18). Ceftazidime, moxalactam, and gentamicin were administered intravenously and enoxacin was administered orally immediately after infection and 6 h later. Immunoglobulin was administered intravenously 1 day before infection; amphotericin B (orally) and miconazole (subcutaneously) were administered four times, immediately and 6, 24, and 30 h after infection. Controls were left unmedicated. Efficacy, expressed as the percentage of survivors, was evaluated 2 weeks postinfection, except for the *P. aeruginosa* infection in normal mice, for which evaluation was made 1 week postinfection. Experiments were repeated at least twice, and the pooled data were used for analysis. Combination effects were regarded as synergistic when the survival percentage for a combination therapy with a dose of rHu IL-1α and a dose of a drug was significantly higher than that of both monotherapies with the same dose of each drug by Fisher's exact method.

RESULTS

Combination effect on *P. aeruginosa* infection. Combination effects of rHu IL-1α with representative antipseudomonal drugs and immunoglobulin were examined in systemic infection with *P. aeruginosa* in mice. As shown in Table 1, none of the unmedicated controls survived. rHu IL-1α alone intramuscularly injected at doses of 0.01 to 1 μg per mouse saved mice from death, with survival rates of 5 to 29%. Intravenous ceftazidime (0.8 to 25 mg/kg) alone, intravenous gentamicin (0.8 to 6.3 mg/kg) alone, oral enoxacin (6.3 to 50 mg/kg) alone, and intravenous immunoglobulin (12.5 to 200 mg/kg) alone showed survival rates of 0 to 25, 0 to 17, 0 to 75,

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TABLE 1. Combination effect of rHu IL-1α and chemotherapeutic drugs on *P. aeruginosa* infection in mice

Drug (mg/kg)	No. of survivors/no. tested (%) with drug plus rHu IL-1α at (μg/mouse):					
	1	0.3	0.1	0.03	0.01	0
Ceftazidime						
25	14/16[a,b] (88)	10/16[a,b] (63)	8/16[a,b] (50)	8/16[a,b] (50)	4/16[b] (25)	2/16 (13)
12.5	14/16[a,b] (88)	8/16[b] (50)	10/16[a,b] (63)	4/16[b] (25)	4/16[b] (25)	4/16 (25)
6.3	14/16[a,b] (88)	7/16[a] (44)	4/16[b] (25)	2/16 (13)	3/16 (19)	1/16 (6)
3.1	12/16[a,b] (75)	6/16[a] (38)	3/16[a] (19)	2/16[a] (13)	0/16[c] (0)	0/16 (0)
1.6	10/16[a,b] (63)	6/16[a] (38)	3/16[a] (19)	2/16[a] (13)	1/16 (6)	0/16 (0)
0.8	10/16[a,b] (63)	6/16[a] (38)	2/16[a] (13)	2/16[a] (13)	1/16 (6)	0/16 (0)
Gentamicin						
6.3	12/16[a,b] (75)	15/16[a,b] (94)	20/24[a,b] (83)	15/24[a,b] (63)	2/16 (13)	4/24 (17)
3.1	9/16[a,b] (56)	8/16[a,b] (50)	12/24[a,b] (50)	8/24[a,b] (33)	3/16 (19)	2/24 (8)
1.6	7/16[a] (44)	2/16[a] (13)	4/24[a] (17)	6/24[a,b] (25)	2/16[a] (13)	0/16 (0)
0.8	3/16[a] (19)	1/16 (6)	1/24 (4)	1/24 (4)	2/16[a] (13)	0/16 (0)
Enoxacin						
50	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)		12/16 (75)
25	16/16[a,b] (100)	16/16[a,b] (100)	12/16[a,b] (75)	11/16[a,b] (69)		4/16 (25)
12.5	8/16 (50)	12/16[a,b] (75)	9/16[b] (56)	7/16[b] (44)		4/16 (25)
6.3	9/16[a,b] (56)	2/16[a] (13)	4/16[a] (25)	4/16[a] (25)		0/16 (0)
Immunoglobulin prepn						
200		14/16[a,b] (88)	8/16[b] (50)	8/16[b] (50)		10/24 (42)
100		14/16[a,b] (88)	6/16[b] (38)	6/16[b] (38)		12/32 (38)
50		13/16[a,b] (81)	3/16 (19)	4/16[b] (25)		9/40 (23)
25		11/16[a,b] (69)	2/16 (13)	4/16[a,b] (25)		1/40 (3)
12.5		7/24[a] (29)	1/16 (6)	1/16 (6)		0/16 (0)
None	16/56 (29)	12/56 (21)	3/56 (5)	3/56 (5)	3/56 (5)	0/56 (0)

[a] Significantly higher than the survival percent for monotherapy with an antibiotic or an immunoglobulin preparation at the corresponding dose ($P < 0.05$).
[b] Significantly higher than the survival percent for monotherapy with rHu IL-1α at the corresponding dose ($P < 0.05$).
[c] Significantly lower than the survival percent for monotherapy with rHu IL-1α at the corresponding dose ($P < 0.05$).

and 0 to 42%, respectively. When mice were treated with both rHu IL-1α and one of the drugs, synergistic effects were observed with all the drug combinations tested at appropriate doses. The results indicate that rHu IL-1α potentiates the therapeutic effect of antipseudomonal drugs and immunoglobulin, irrespective of their mechanisms of action. The survival kinetics of mice treated with rHu IL-1α alone, enoxacin alone, and combinations of rHu IL-1α and enoxacin are shown in Fig. 1. Most unmedicated control mice died within 1 day, and none survived by 3 days postinfection. The survival percentages of mice treated with rHu IL-1α alone or enoxacin alone were more or less increased dose relatedly. The survival percentages of mice treated with both rHu IL-1α and enoxacin were much higher than those of mice treated with both monotherapies. In the groups treated with enoxacin monotherapy and combination therapy with a fixed dose of rHu IL-1α (0.1 μg per mouse) and various doses of enoxacin, death occurred even after 3 days postinfection, indicating that the treatments delayed the mortal course of infection but were not sufficient to save mouse life, especially at lower doses. However, survivors 6 days postinfection did not die later.

Combination effect on *C. albicans* infection. In systemic *C. albicans* infection in mice (Table 2), the survival rate of unmedicated controls was 6%. rHu IL-1α alone intramuscularly injected at doses of 0.01 to 0.3 μg per mouse showed survival rates of 0 to 50%. Six to 38% of mice given amphotericin B alone orally at doses of 0.05 to 0.2 mg/kg and 13 to 19% of mice given miconazole alone subcutaneously at doses of 0.4 to 6.3 mg/kg survived under the experimental conditions used. When combination therapy of rHu IL-1α and amphotericin B or miconazole was performed, its survival percentages were generally higher than those of each monotherapy at higher doses but not significantly different from those of rHu IL-1α monotherapy, except in a few cases. This result suggests that rHu IL-1α weakly augments the therapeutic effect of antifungal drugs on *C. albicans* infections. The survival kinetics are shown in Fig. 2. Unmedicated mice died sporadically within 7 days. Monotherapy with rHu IL-1α or amphotericin B brought about an increase in survival and a prolongation of survival days dose relatedly, and combination therapy with rHu IL-1α and amphotericin B exhibited better therapeutic accomplishments than did each monotherapy. Death was observed throughout 14 days of observation even in medicated groups, suggesting that complete cure is difficult to attain in this infection model.

Combination effect on *K. pneumoniae* infection. In the two infection models discussed above, rHu IL-1α was administered before infection and combination drugs were administered after infection. In the *K. pneumoniae* infection in mice (Table 3), both rHu IL-1α and combination drugs were administered postinfection. None of the unmedicated mice survived in this model. The survival rates of mice treated with intramuscular rHu IL-1α (0.03 to 0.3 μg per mouse) alone, intravenous moxalactam (0.1 to 3.1 mg/kg) alone, intravenous gentamicin (0.025 to 0.4 mg/kg) alone, oral enoxacin (0.8 to 6.3 mg/kg) alone, and intravenous immunoglobulin (25 to 200 mg/kg) alone were 7 to 32, 0 to 48, 0 to 88, 0 to 56, and 0 to 13%, respectively. In contrast, synergistic effects were observed with combination treatments with rHu IL-1α and the drugs. As shown in Fig. 3, all unmedicated mice had died 3 days postinfection. Monotherapy with rHu IL-1α or moxalactam delayed the occurrence of death dose

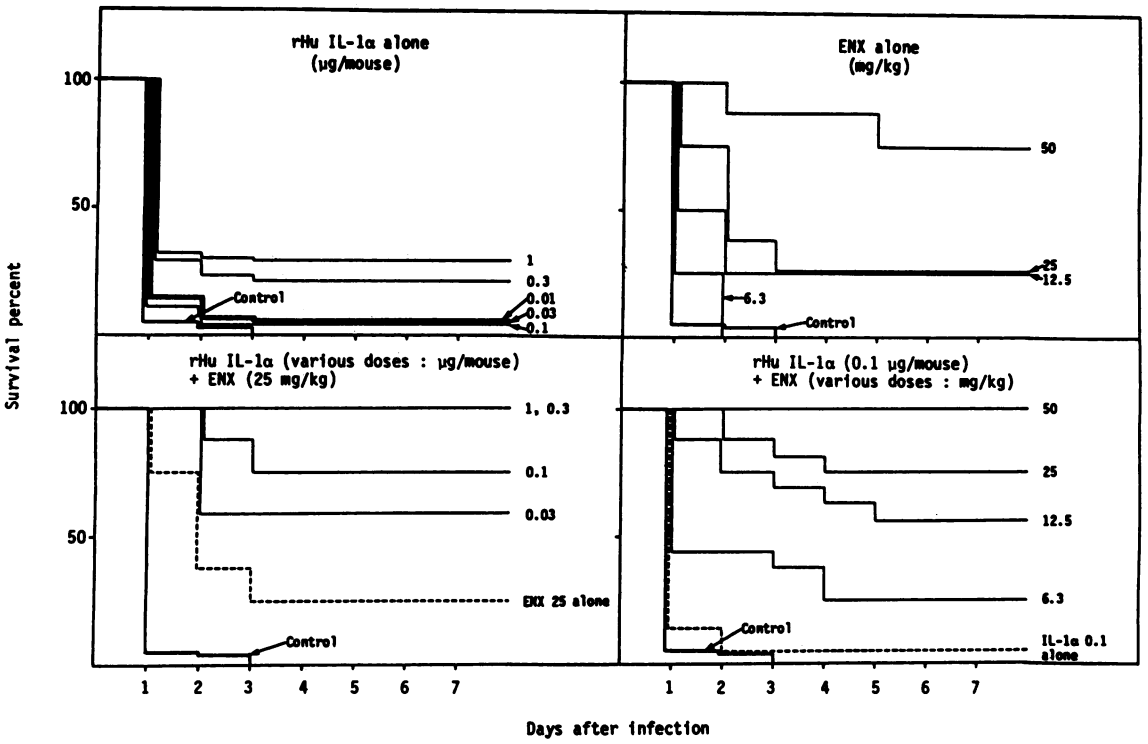

FIG. 1. Survival kinetics of mice infected with *P. aeruginosa* and treated with rHu IL-1α alone, enoxacin (ENX) alone, or combinations of rHu IL-1α and enoxacin.

relatedly, and survival percentages were high in the decreasing order of the doses used. Combination therapy with rHu IL-1α and moxalactam showed much higher survival percentages than did each monotherapy, and death was rare after 1 week, suggesting that most survivors were cured of infection completely.

Combination effect on *P. aeruginosa* infection in leukopenic mice. The combination effect was examined in *P. aeruginosa* infection in mice with leukopenia induced by cyclophosphamide administration (Table 4). The survival rates were 6% for unmedicated controls and 6 to 56, 0 to 88, and 13 to 75% for groups of mice treated with intramuscular rHu IL-1α (0.001 to 0.1 μg per mouse) alone, intravenous gentamicin (1.6 to 12.5 mg/kg) alone, and intravenous immunoglobulin (1.6 to 12.5 mg/kg) alone, respectively. Combination therapy with rHu IL-1α and gentamicin or immunoglobulin showed significantly higher survival percentages than did each monotherapy, indicating that a synergistic effect of rHu IL-1α and chemotherapeutic drugs occurred even with leukopenic mice. Examples of the survival kinetics are shown in Fig. 4. Unmedicated mice died sporadically over the observation period of 14 days. Mice treated with rHu IL-1α alone, gentamicin alone, or combinations of rHu IL-1α and gentamicin also died sporadically throughout 14 days, although their survival percentages were generally high, depending on the doses used. This result was in contrast with that shown in Fig. 1; in that experiment, the same infecting organism was used but no mice died after 6 days postinfec-

TABLE 2. Combination effect of rHu IL-1α and antifungal drugs on *C. albicans* infection in mice

Drug (mg/kg)	No. of survivors/no. tested (%) with drug plus rHu IL-1α at (μg/mouse):				
	0.3	0.1	0.03	0.01	0
Amphotericin B					
0.2	13/16[a] (81)	12/16[a] (75)	11/16 (69)	11/16[b] (69)	6/16 (38)
0.1	13/16[a] (81)	8/16[a] (50)	9/16[a] (56)	5/16[b] (31)	1/16 (6)
0.05	11/16[a] (69)	8/16[a] (50)	8/16[a] (50)	3/16[b] (19)	1/16 (6)
Miconazole					
6.3	12/16[a] (75)	12/16[a] (75)	12/16[a,b] (75)	6/16[b] (38)	3/16 (19)
3.1	11/16[a] (69)	9/16[a] (56)	5/16 (31)	5/16[b] (31)	2/16 (13)
1.6	10/16[a] (63)	9/16[a] (56)	5/16 (31)	7/16[b] (44)	2/16 (13)
0.8	6/16 (38)	7/16 (44)	5/16 (31)	8/16[a,b] (50)	2/16 (13)
0.4	9/16[a] (56)	8/16[a] (50)	7/16 (44)	6/16[b] (38)	2/16 (13)
None	8/16 (50)	7/16 (44)	6/16 (38)	0/16 (0)	1/16 (6)

[a] See footnote *a* to Table 1.
[b] See footnote *b* to Table 1.

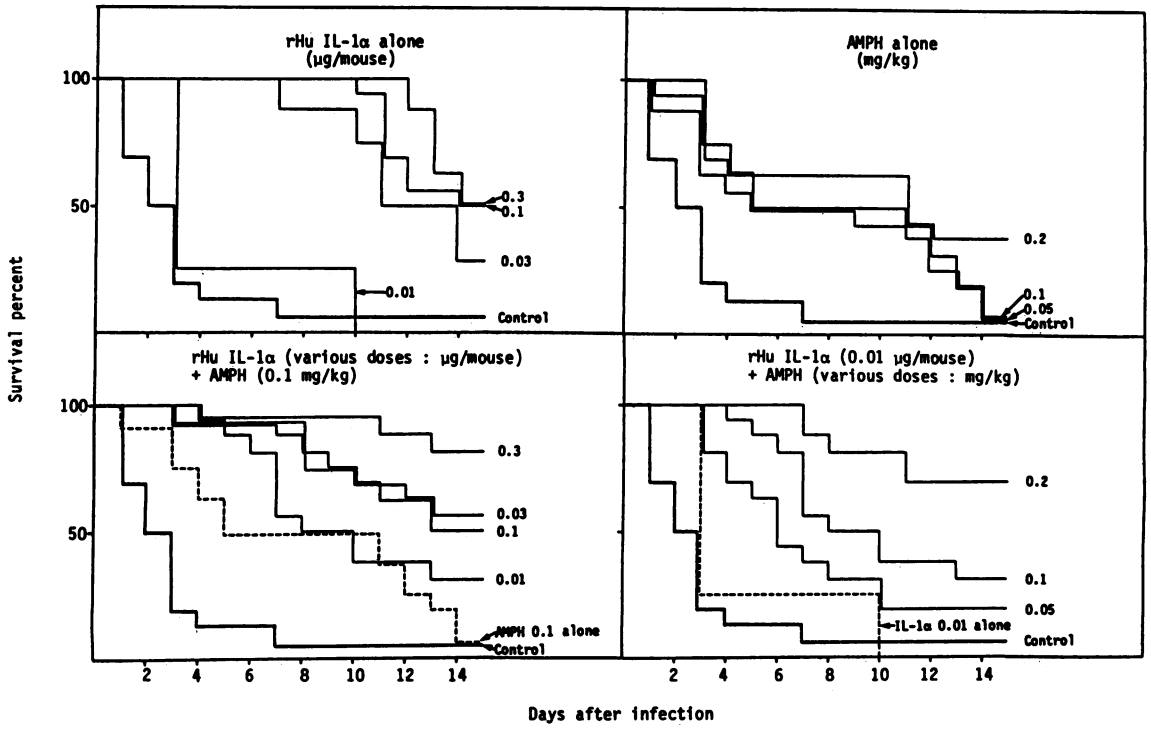

FIG. 2. Survival kinetics of mice infected with *C. albicans* and treated with rHu IL-1α alone, amphotericin B (AMPH) alone, or combinations of rHu IL-1α and amphotericin B.

TABLE 3. Combination effect of rHu IL-1α and chemotherapeutic drugs on *K. pneumoniae* infection in mice

Drug (mg/kg)	No. of survivors/no. tested (%) with drug plus rHu IL-1α at (μg/mouse):			
	0.3	0.1	0.03	0
Moxalactam				
3.1	16/16[a,b] (100)	16/16[a,b] (100)	10/16[b] (63)	19/40 (48)
1.6	16/16[a,b] (100)	16/16[a,b] (100)	8/24[b] (33)	11/40 (28)
0.8	23/24[a,b] (96)	15/16[a,b] (94)	9/32[b] (28)	3/32 (9)
0.4	16/16[a,b] (100)	15/16[a,b] (94)	9/32[a,b] (28)	0/16 (0)
0.2	10/16[a,b] (63)	4/16[a] (25)	4/16[a] (25)	0/16 (0)
0.1	4/16[a] (25)	2/16[a] (13)	2/16[a] (13)	0/16 (0)
Gentamicin				
0.4	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)	14/16 (88)
0.2	16/16[a,b] (100)	12/16[a,b] (75)	12/16[a,b] (75)	3/16 (19)
0.1	12/16[a,b] (75)	2/16 (13)	0/16[c] (0)	1/16 (6)
0.05	7/16[a] (44)	0/16[c] (0)	0/16[c] (0)	0/16 (0)
0.025	4/16[a] (25)	0/16[c] (0)	0/16[c] (0)	0/16 (0)
Enoxacin				
6.3	16/16[a,b] (100)	16/16[a,b] (100)	8/16[b] (50)	9/16 (56)
3.1	17/24[a,b] (71)	12/24[a,b] (50)	5/32 (16)	1/24 (4)
1.6	7/24[a] (29)	2/24[a] (8)	2/24[a] (8)	0/24 (0)
0.8	2/24[a,c] (8)	1/24 (4)	0/24[c] (0)	0/16 (0)
Immunoglobulin prepn				
200	10/16[a,b] (63)	8/16[a,b] (50)	8/16[a,b] (50)	2/16 (13)
100	8/16[a] (50)	8/16[a,b] (50)	6/16[b] (38)	2/16 (13)
50	8/16[a] (50)	4/16 (25)	4/16 (25)	2/16 (13)
25	2/16[a] (13)	2/16[a] (13)	2/16[a] (13)	0/16 (0)
None	18/56 (32)	7/56 (13)	4/56 (7)	0/64 (0)

[a] See footnote *a* to Table 1.
[b] See footnote *b* to Table 1.
[c] See footnote *c* to Table 1.

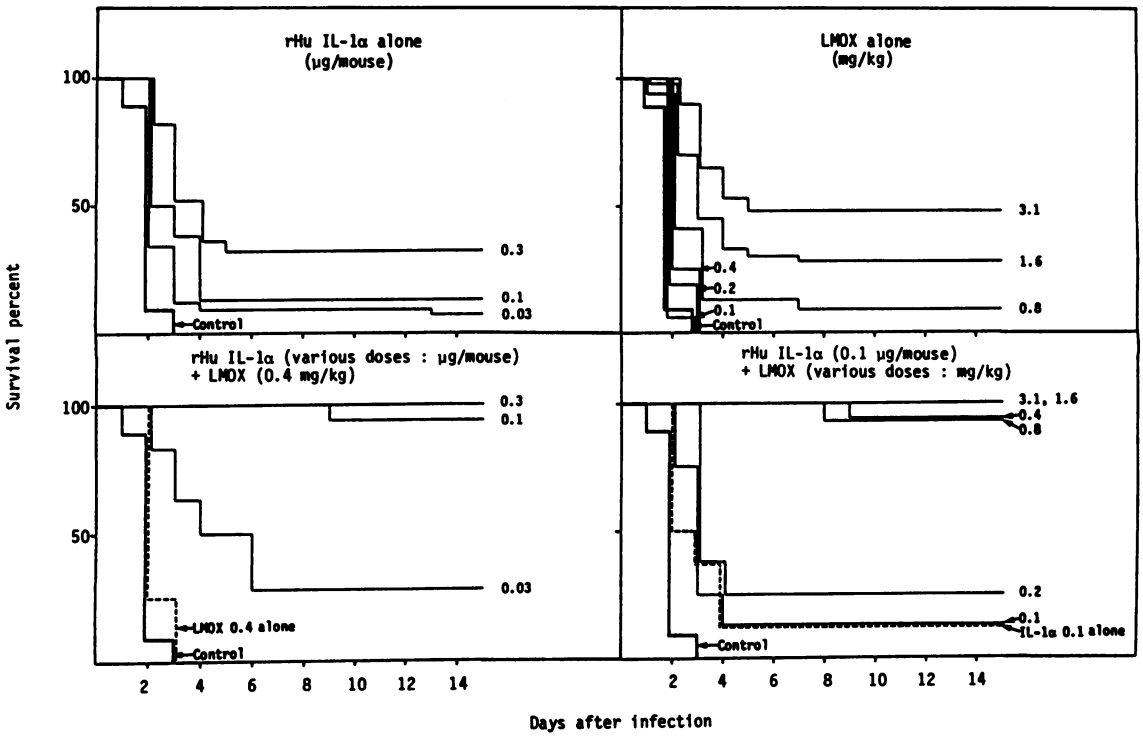

FIG. 3. Survival kinetics of mice infected with *K. pneumoniae* and treated with rHu IL-1α alone, moxalactam (LMOX) alone, or combinations of rHu IL-1α and moxalactam.

tion. This suggests that survivors in a leukopenic state are not cured completely.

DISCUSSION

The present study revealed that combination therapy with rHu IL-1α and chemotherapeutic drugs was generally synergistic in systemic infections in mice. Favorable effects were observed at rHu IL-1α doses as low as 1 to 30 ng per mouse, which were lower than 1/100,000 to 1/3,000 of its 50% lethal dose (15). The chemotherapeutic drugs used in combination with rHu IL-1α were cephalosporin, aminoglycoside, and quinolone derivatives and an immunoglobulin preparation. Since synergism was observed with most combinations tested, chemotherapeutic agents with various mechanisms of action seem to be compatible with rHu IL-1α.

Potentiation of the chemotherapeutic effect by rHu IL-1α was more or less observed in all the infection models tested here. Since rHu IL-1α augments host resistance to infections caused by *P. aeruginosa*, *K. pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Salmonella typhimurium*, and *C. albicans* in mice (10), it is likely that combination therapy of rHu IL-1α and chemotherapeutic drugs is preferable in infections caused by various organisms.

The oral efficacy of amphotericin B may need some

TABLE 4. Combination effect of rHu IL-1α and chemotherapeutic drugs on *P. aeruginosa* infection in leukopenic mice

Drug (mg/kg)	No. of survivors/no. tested (%) with drug plus rHu IL-1α at (μg/mouse):					
	0.1	0.03	0.01	0.003	0.001	0
Gentamicin						
12.5	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)	16/16[a,b] (100)	14/16 (88)
6.3	14/16[a] (88)	14/16[a,b] (88)	14/16[a,b] (88)	12/16[b] (75)	12/16[b] (75)	7/16 (44)
3.1	14/16[a] (88)	11/16[a,b] (69)	7/16[b] (44)	5/16 (31)	4/16 (25)	5/16 (31)
1.6	8/16[a] (50)	5/16[a] (31)	2/16[a] (13)	7/16[a,b] (44)	4/16[a] (25)	0/16 (0)
Immunoglobulin prepn						
12.5	16/16[a,b] (100)	16/16[a,b] (100)	14/16[b] (88)	10/16[b] (63)	12/16[b] (75)	12/16 (75)
6.3	14/16[a] (88)	8/16[b] (50)	10/16[b] (63)	7/16[b] (44)	7/16[b] (44)	5/16 (31)
3.1	6/16 (38)	2/16 (13)	4/16 (25)	5/16 (31)	2/16 (13)	2/16 (13)
1.6	6/16 (38)	2/16 (13)	3/16 (19)	2/16 (13)	7/16[b] (44)	2/16 (13)
None	9/16 (56)	1/16 (6)	1/16 (6)	1/16 (6)	1/16 (6)	1/16 (6)

[a] See footnote *a* to Table 1.
[b] See footnote *b* to Table 1.

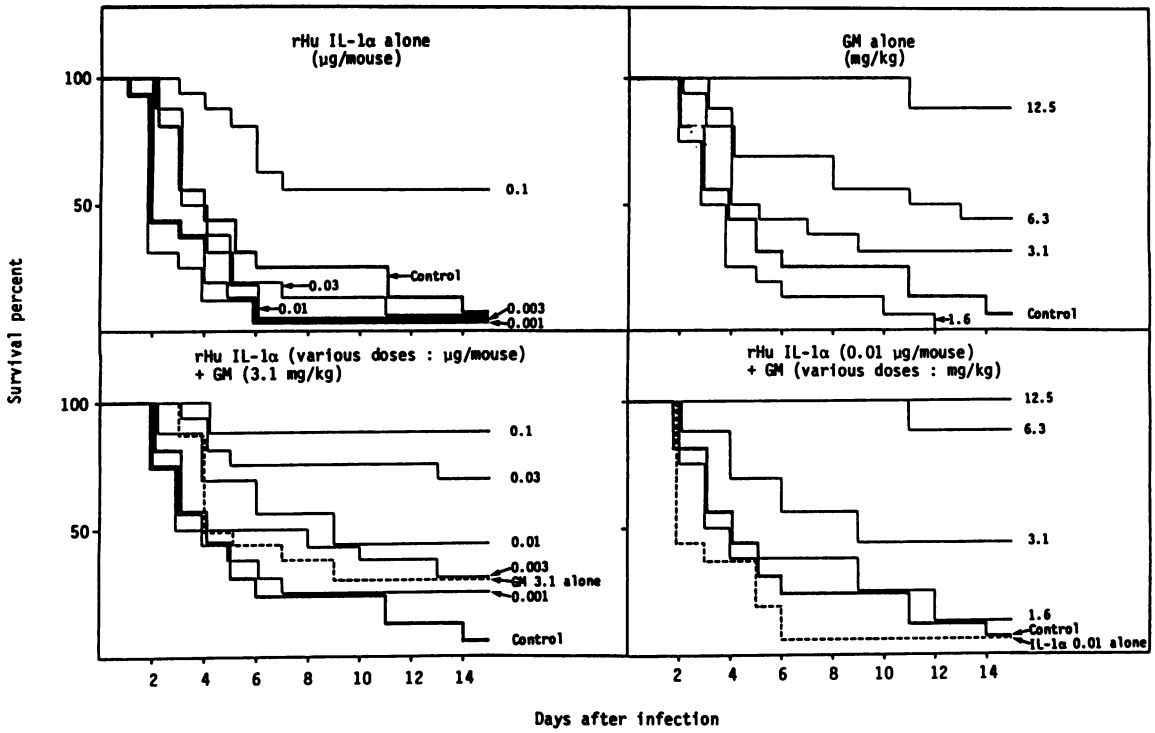

FIG. 4. Survival kinetics of leukopenic mice infected with *P. aeruginosa* and treated with rHu IL-1α alone, gentamicin (GM) alone, or combinations of rHu IL-1α and gentamicin.

explanation because it is well-known that the drug is poorly absorbed when administered orally. However, this fact does not necessarily mean that orally administered amphotericin B is ineffective against systemic fungal infections. It has high antifungal potency in vitro, and levels in plasma are sufficiently high in humans given large oral doses (14, 19). It was previously reported that oral amphotericin B is effective clinically against chronic mucocutaneous candidiasis (12) and liver abscess caused by *C. albicans* (17). We confirmed the oral efficacy of amphotericin B against *C. albicans* infection in mice, as shown in Fig. 2. Since death owing to toxicity was rare upon oral administration of amphotericin B, compared with intravenous administration, amphotericin B was administered orally in combination with intramuscular rHu IL-1α in this experiment. The finding that combination therapy with rHu IL-1α and amphotericin B or miconazole generally showed higher survival percentages than did each monotherapy was noteworthy, since most antifungal agents are insufficient in efficacy.

Troublesome infections not successfully treated with antimicrobial agents alone often occur in immunocompromised patients. In the present study, the combination therapy of rHu IL-1α with chemotherapeutic drugs was synergistic in *P. aeruginosa* infection in mice with cyclophosphamide-induced leukopenia, in which the number of leukocytes in peripheral blood was only about 1/10 that in normal mice at the time of infection, irrespective of rHu IL-1α administration (10). Van der Meer et al. reported that rHu IL-1β pretreatment combined with gentamicin treatment postinfection protects granulocytopenic mice against lethal pseudomonal infection (22). They did not find a difference in the numbers of blood granulocytes; in the numbers of bacteria in the blood, thigh muscle, liver, spleen, and kidneys; or in superoxide production by peritoneal macrophages between rHu IL-1β-treated and control mice and supposed that protection by rHu IL-1β would occur through a noncellular mechanism. Their and our results suggest that the favorable combination effect of rHu IL-1α and antimicrobial agents in leukopenic mice cannot be simply accounted for by recovery in the number of leukocytes, although such recovery through the stimulation of granulopoiesis by rHu IL-1α (1, 5) is an important factor in the enhancement of antibacterial resistance in leukopenic mice (9). The kinetic data showed that combination therapy with rHu IL-1α and antimicrobial agents brought about almost complete cure of *P. aeruginosa* and *K. pneumoniae* infections in normal mice but did not cause complete cure of *C. albicans* infection in normal mice or of *P. aeruginosa* infection in leukopenic mice. It has been reported that *P. aeruginosa* and *K. pneumoniae* are ingested and killed mainly by polymorphonuclear cells (6, 21), while *C. albicans* is killed by polymorphonuclear cells and activated macrophages via T-cell-mediated immunity (11). Therefore, it is possible that the killing activity of preexisting polymorphonuclear cells is enhanced by rHu IL-1α and cooperated with bactericidal activity of antimicrobial agents. It has been shown that IL-1 induces the release of specific granule contents from neutrophils (7, 20) and stimulates neutrophil oxygen-dependent metabolism (8). rHu IL-1α may activate macrophages less efficiently, if at all, than polymorphonuclear cells under the present experimental conditions, as suggested by van der Meer et al. (22).

Obstinate infections sometimes occur in myelosuppressed cancer patients. It may be worth pointing out that rHu IL-1α has antitumor activity (15, 16) and restorative activity from myelosuppression induced by cyclophosphamide (1, 2) or 5-fluorouracil (13). These activities and the favorable combination effect of rHu IL-1α and antimicrobial agents shown here seem to be desirable for the treatment of infections in cancer patients given myelosuppressive antitumor drugs.

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