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Original Article

Comparison of Empiric Antibiotic Escalation Therapy with Vancomycin (VAN) versus Linezolid (LIN) in Patients with Febrile Neutropenia

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Abstract. ***Background:*** **In febrile neutropenia, either linezolid (LIN) or vancomycin (VAN) can be used if a gram-positive infection is suspected. Interestingly there is no literature in which both are compared in the setting of febrile neutropenia. Therefore, we provide here the results of a retrospective analysis of adding VAN versus LIN in patients with febrile neutropenia.**
Methods: **Patients with haematological diseases and febrile neutropenia after myelosuppressive chemotherapy and no clearance of infection after the first empiric broad-spectrum antibiotic were escalated to VAN or LIN from 03/2010 to 03/2014 at the University Hospital Bonn were included in this retrospective analysis.**
Results: **Out of the 73 patients, 50 had received VAN and 23 LIN. The median hospitalisation time in the LIN cohort was significantly shorter than in the VAN cohort (LIN 16 days vs VAN 20 days p=0.046). Successful defervescence with the escalation to VAN or LIN could be detected in 76% of the LIN cases and 50% in the VAN group (p=0.052). This trend to better efficacy with LIN was also shown by a higher rate of discontinuation of VAN and escalation to another antibiotic scheme (54.2%) than in the LIN cohort (24%, p=0.052).**
Conclusion: **The antibiotic therapy in febrile neutropenia with LIN showed a trend of better efficacy than therapy with VAN. However, because of the small sample size and the retrospective manner, VAN may still be considered a reasonable option in neutropenic fever, and randomised studies are needed in this field.**

Keywords: Neutropenic fever; Antibiotic escalation; Bacteria; Infection.

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Introduction. Patients undergoing myelosuppressive chemotherapy are at high risk for infections, possibly leading to life-threatening complications and, therefore, a major cause of morbidity and mortality.[1] Leukocytes are an important aspect of bacterial clearance. The bacterial clearance is disturbed during myelosuppression, which leads to neutropenia, opening the door for severe bacterial infection.

Neutropenia is defined as absolute neutrophils (ANC) < 500/µl for 48h.[2] It is important to consider severe

neutropenia a medical emergency because the severe immunocompromised patient is highly likely to develop sepsis out of a simple infection. Neutropenia is classified into different risk groups depending on how long the duration of neutropenia is expected. With the increasing duration of neutropenia, the risk of developing severe infections is also increasing.[3]

The duration of neutropenia depends on the tumour type and the given chemotherapy. For example, patients with haematological diseases have a higher risk for prolonged neutropenia and risk of infections than patients with solid tumours.[4]

If an infection occurs with fever or other signs of infection during neutropenia, it is called febrile neutropenia. The incidence of febrile neutropenia in patients with haematological diseases is about 70-80%;[5] in patients with solid tumours, it is far below (10-50%).[2,6]

Febrile neutropenia needs immediate empirical antibiotic treatment because of the risk of mortality.[2,7]

The ECIL guidelines recommend that if a gram-positive is likely the reason to add an appropriate agent to the already empiric therapy, the AGIHO (Infectious disease working party of the German Society of Haematology and Medical Oncology (DGHO)) explicitly recommends the adding of linezolid if there is a suspicion for a gram-positive infection (like mucositis, or catheter-infection).[3,8] If a gram-positive infection is suspected beneath linezolid, vancomycin can also be a valid option, most commonly used over many years, but it has to keep in mind that vancomycin is not working in VRE (vancomycin-resistant *enterococc*i).

One important difference between the two antibiotic therapies is that linezolid is only bacteriostatic, and vancomycin is a bactericide. Therefore, it is very interesting if there is a difference in the efficacy in a high risk setting like febrile neutropenia between these two therapies. Interestingly there is no literature in which vancomycin and linezolid are compared in the setting of febrile neutropenia in the presence of a suspected gram-positive bacteria. Therefore, we provide the results obtained from a retrospective analysis of the two regimes adding VAN versus LIN in patients with febrile neutropenia and suspected gram-positive infection. We compare the efficacy of the two regimens with regard to the incidence of fever, microbiologically documented infections, infection-related deaths and differences in the bacterial species detected.

Materials and Methods.

Study population. Patients with febrile neutropenia after myelosuppressive chemotherapy because of a haematological disease and no clearance of infection after the first empiric broad-spectrum antibiotic were escalated to VAN or LIN from 03/2010 to 03/2014 at the University Hospital Bonn were included in this retrospective cohort study. Neutropenia was defined as leukocytes < 1G/l or neutrophile granulocytes < 0,5G/l. All included patients had fever >38°C and age > 18 years. Patients with known allergy to VAN or LIN were excluded.

The data collection was done by a standard questionnaire, which contained baseline characteristics like sex, age, disease status, type of infection, days of fever, laboratory results, medication and other variables and was already used in another publication.[9]

Treatment protocol. All included patients had a fever in neutropenia and showed treatment failure of the initial empiric therapy, e.g. ongoing fever after at least three days of initial antibiotic treatment or clinical worsening irrespective of the duration of first-line therapy with signs of a suspected gram-positive infection. Therefore, they were escalated to VAN or LIN either as monotherapy or in combination with another broad-spectrum antibiotic. The judgment for VAN or LIN was done by the physician's clinical decision.

Antibiotic prophylaxis was cotrimoxazole 960 mg twice weekly and ciprofloxacin 500mg twice daily.

If fever in neutropenia occurred, the antibiotic prophylaxis was stopped, and a broad-spectrum antibiotic, usually tazobactam/piperacillin 3x4,5g daily or meropenem 3x1g daily, was initiated.

Patients who switched from VAN to LIN or LIN to VAN during their treatment phase were still registered in the antibiotic group, which they received as the first escalation scheme.

VAN was given as a bolus infusion (1g every 12h), and drug levels were monitored routinely at least every second day. The dose of vancomycin was reduced or increased if necessary to maintain drug trough concentrations between 5-15mg/l. If oral administration was possible, LIN was also given as a bolus infusion 2 times a day (600mg) or orally b.i.d. (600mg).

Definitions of endpoints. Successful antibiotic therapy was defined as defervescence for at least seven days without any sign of continuing infection. Treatment failure was defined if there was fever persistence longer than 72-96h after starting VAN or LIN.

Febrile episodes were classified as fever of unknown origin (FUO), pneumonia (radiologically confirmed) and non-pneumonic microbiologically documented infection (MDI) and/or clinically documented infection (CDI).

Microbiologically documented infections were defined as infections with the occurrence of fever and evidence for bacteria or viral or fungal pathogens detected in normally sterile body sites. *Staphylococci* or *Micrococci* were only classified as a cause of infection if detected at least two times in sterile body sites.

Clinically documented infections such as venous line, soft tissue, and gastrointestinal infections were assumed when the patient had typical clinical infection symptoms

but no proof of microbial pathogens in the collected specimen. Additionally, in the absence of a positive microbiological specimen, pneumonia was defined as fever with infiltrates in radiologic imaging.

Side effects were classified according to CTCAE-version 4.03. An adverse event of special interest was nephrotoxicity, which was documented by monitoring the serum creatinine and glomerular-filtration rates (GFR) before, during and after the therapy with VAN or LIN.

Costs of treatment. All course costs on the ward were obtained by analysing the different therapies' costs based on the DRG, OPS. Also the costs of the antibiotic treatment with VAN or LIN from the first day of VAN or LIN were calculated using the prices of the hospital pharmacy, incl. VAT.

Ethical considerations. All study investigators were staff of Department III of Internal Medicine. Because of the retrospective manner, no interventions were performed as part of the study. Instead, patient care, data collection and analysis were performed by site personnel using current techniques of privacy assurance. In Northrhine-Westphalia state, Germany, neither an Ethics Committee's approval nor patient consent is necessary.

Statistical analysis. Mann-Whitney U, Fisher's exact, Chi-Square tests were used to test for differences as indicated in the results section. A two-sided p-value below 0.05 was considered statistically significant. Statistical analyses were performed by SPSS Statistics Version 21 (IBM Corp., Armonk, NY).

Results.

Study population. In the retrospective analysis, 84 episodes of fever in 73 patients could be analysed. In all these cases, the patients had received myelosuppressive chemotherapy because of haematological malignancy and experienced fever in neutropenia, which was treated with a broad-spectrum antibiotic. Because of treatment failure, the antibiotic therapy was escalated to VAN or LIN because of suspected gram-positive bacteria.

Out of the 73 patients, 50 had received VAN and 23 LIN. In 2/3 of all patients, the underlying malignancy was AML (acute myeloid leukaemia) (VAN 62%, LIN 70%), followed by a Non-Hodgkin-Lymphoma (VAN 18%, LIN 9%). Also, patients with acute lymphatic leukaemia (ALL) and multiple myeloma (MM) were included (**Table 1**).

About half of the patients in both cohorts were female (VAN 40%, LIN 48%, p=0.613), and the median age was 57 years (VAN IQR 49-62 years, LIN 33-69 years, p=0.512). Also, there was no difference in patients aged >60 years in both treatment groups (40%). In addition, there were no significant differences in cardiovascular or pulmonary comorbidities. Patient characteristics are shown in **Table 1**.

Table 1. Patient characteristics.

	All patients n=73	**VAN n=50**	**LIN n=23**	**p**
Women	31 (42.5 %)	20 (40.0 %)	11 (47.8 %)	0.613
Age (years)				
Median	57	58	54	0.512
IQR[1]	47-63	49-62	33-69	
Age > 60 years	29 (39.7 %)	20 (40 %)	9 (39.1 %)	1.000
comorbidities				
CHD[2]	17 (23.3 %)	10 (20 %)	7 (30.4 %)	0.378
Arterial Hypertension	18 (24.7 %)	14 (28 %)	4 (17.4 %)	0.393
Pulmonary	9 (12 %)	6 (12 %)	3 (13 %)	0.587
Diabetes mellitus	5 (6.8 %)	3 (6.0 %)	2 (8.7 %)	0.647
Malignant disease				
AML[3]	47 (64.4 %)	31 (62.0 %)	16 (69.6 %)	0.844
ALL[4]	6 (8.2 %)	4 (8.0 %)	2 (8.7 %)	
MM[5]	7 (9.6 %)	5 (10.0 %)	2 (8.7 %)	
NHL[6]	11 (15.1 %)	9 (18.0 %)	2 (8.7 %)	
Others[7]	2 (2.7 %)	1 (2.0 %)	1 (4.3 %)	
Duration of neutropenia in days				
Median (days)	16	17	15	0.955
IQR[1]	10-25	10-27	10-24	
[3] 10 days	57 (78.1)	39 (78.0 %)	18 (78.3 %)	1.000
Treatment with growth factors	39 (53.4%) %)	28 (56,0 %)	11 (47,8 %)	0.616

[1]IQR: Inter Quartile Range [2]CHD: chronic heart disease [3]AML: acute myeloid leukaemia, [4]ALL: acute lymphoblastic leukaemia, [5]MM: multiple myeloma [6]Non-Hodgkin-Lymphoma [7]M.Hodgkin.

The median duration of neutropenia was not significantly different between the VAN and the LIN group, but there was a trend to a slightly shorter duration in the LIN group (LIN 15 days, VAN 17 days p=0.955).

Treatment cases. As already described, 73 patients could be included in this retrospective analysis. These 73 patients experienced 84 neutropenic fever events, for which they received 59 VAN treatments and 25 LIN as escalation therapy because of persistent infection.

Same as for patient data, there were no significant differences in age, sex, comorbidities, underlying disease, and remission status in the treatment cases between the VAN and LIN groups (data not shown).

One significant difference was that in the LIN group were significantly more treatment cases with an elevated serum-creatinine (>1,3mg/dl) before the start of the escalated antibiotic therapy (LIN n=4, VAN n=1, p=0.026).

In nearly all cases in both groups, either VAN or LIN were given in combination with another broad-spectrum antibiotic therapy (VAN n=53, 89,9%, LIN n=23, 92%, p=0.633). In almost all cases the combination partner was meropenem (VAN=45, 84,7%, LIN n=19, 82,6%), followed by fosfomycin as partner (VAN n=2, 3,8%, LIN n=2, 8,7%), further antibiotics were metronidazole, tazobactam/piperacillin, fosfomycin and clarithromycin in some cases (p=0.490).

In about 10% in both treatment groups, an antimycotic drug was added (VAN n=8, 10%, LIN n=3, 12%, p=1.0).

In most cases, VAN or LIN was added as the first escalation of antibiotic treatment (level 2, VAN n=53, 89,8%, LIN n=21, 84%).

Efficacy. Successful defervescence with the escalation to VAN or LIN could be detected in 76% of the LIN cases and 50% in the VAN group (p=0.052). This trend to better efficacy with LIN was also shown by a higher rate of the discontinuation of VAN and escalation to another antibiotic scheme in the VAN group (54.2%) than in the LIN cohort (24%, p=0.052).

Probably because of the higher rate of further change in the antibiotic strategy in the VAN group, the median duration of total antibiotic treatment was significantly longer in the VAN than in the LIN cohort (VAN 9 days, LIN 7 days, p=0.029).

The median duration of the application of VAN or LIN in the two cohorts is not significantly different (VAN 6 days, LIN 7 days, p=0.269).

The median time of hospitalisation in the LIN cohort was significantly shorter than in the VAN cohort (LIN 16 days (IQR 11-21) vs VAN 20 days (IQR13-28), p=0.046). When only the days were counted since the antibiotic therapy with VAN or LIN was started, there was still a trend to a shorter hospitalisation time in the LIN treated patients, but this was not significant (LIN 12 days (IQR 8-18), VAN 16 days (IQR 11-22), p=0.109). Also, in the duration of the whole episode of fever (first day of fever until the 7th fever-free day), there was a trend for a shorter median duration in the LIN group than in the patients who received vancomycin as escalation, but this was also not significant (LIN 11 days (IQR 9-16), VAN 13 days (IQR10-19), p=0.113). The median of fever days after the escalation to VAN or LIN was also not statistically different (LIN 2 days (IQR 1-5), VAN 3 days (IQR 1-6), p=0.176 (**Table 2**).

Table 2. Treatment efficacy.

	All episodes n=84	**VAN n=59**	**LIN n=25**	**p**
Median time of hospitalisation since beginning of fever (days, IQR)	19 (12-25)	20 (13-28)	16 (11-21)	0.046
Median time of hospitalisation since VAN/LIN start (days, IQR)	15 (10-22)	16 (11-22)	12 (8-18)	0.109
Median days of fever (days, IQR)	5 (3-8)	5 (3-8)	4 (3-7)	0.469
Median days of fever since start VAN/LIN (days, IQR)	3 (1-6)	3 (1-6)	2 (1-5)	0.176
Median duration of fever (Days, IQR)	13 (10-18)	13 (10-19)	11 (9-16)	0.113

IQR: Inter quartal range

Microbiologically documented infections (MDI). A bacterial pathogen could be found in about half of the fever episodes (VAN n=31, 52.5%, LIN n=10, 40%, p=0.914). In the differentiation in both treatment groups most of the bacterial cases were gram-positive (VAN n=26, 83.9%, LIN n=10, 100%, p=1.0). Most of the gram-positive detected species were *Staphylococcus spp* (VAN n=19, 32.2%, LIN n=5, 20%), followed by *Streptococcus spp* (VAN n=3, 5.1%, LIN n=2, 8%). In the VAN treatment group, one case was a vancomycin-resistant *enterococcus*.

There were no significant differences in both treatment groups regarding the bacterial species, Glycopeptide-sensibility or gram-differentiation (**Table 3**).

Clinically documented infections (CDI). Eleven fever episodes in the VAN and 2 in the LIN cohort showed no

clinical infection focus (VAN 18.6%, LIN 8,0%, p=0.914).

About 40% in both groups showed bacteriaemia (VAN n=22, 37.3%, LIN n=10, 40%). In the LIN treated group there were significant more pneumonias (VAN n=16, 27.1%, LIN n=15, 60%, p=0.006). Around 10% of the treated cases had mould pneumonia (VAN n=5, 8.5%, LIN n=3, 12%). Clinical central venous catheter infections in both treatment groups were detected in around 20% of cases (VAN n=15, 25.4%, LIN n=4, 16%). Only a few gastrointestinal infections could be detected in both groups (in the VAN group 2 cases, one of these was a clostridium difficile infection. In the LIN group, we found one gastrointestinal infection without C. diff detection (**Table 3**).

Table 3. MDI (microbiologically documented infections) and CDI (clinically documented infections).

	Total n=84	VAN n=59	LIN n=25	p
MDI	41 (48.8%)	31 (52,5%)	10 (40.0%)	0.914
Gram-staining				
- gram-positive	36 (82.9%)	26 (83.9%)	10 (100 %)	1.000
- gram-negative	2 (4.9%)	2 (6.5%)	0	
Pathogens:				0.553
Staphylococcus	24 (28.6%)	19 (32.2%)	5 (20%)	
Streptococcus	5 (5.9%)	3 (5.1%)	2 (8%)	
Enterococcus	4 (4.8%)	2 (3.4%)	2 (8%)	
VRE	1 (1.2%)	1 (1.7%)	0	
Micrococcus	1 (1.2%)	0	1 (4%)	
Clostridium difficile	1 (1.2%)	1 (1.7)	0	
Escherichia coli	2 (2.4%)	2 (3.4%)	0	
viral or fungal pathogen	3 (3.6%)	3 (5.1%)	0	
Glycopeptide-sensible gram-positive bacteria	33 (80.5%)	23 (74.2%)	10 (100%)	0.433
CDI				
Pneumonia	31 (36.9%)	16 (27.1%)	15 (60.0%)	0.006
Fungal pneumonia	8 (9.5%)	5 (8.5%)	3 (12%)	0.690
Bacteriaemia	32 (38.1%)	22 (37.3%)	10 (40%)	
CVC-infection	19 (22.6%)	15 (25.4%)	4 (16%)	
Gastrointestinal infection	3 (3.6%)	2 (3.4%)	1 (4%)	
Empyema	5 (6%)	4 (6.8%)	1 (4%)	

VRE: vancomycin resistant enterococcus, Micrococcus: Rothia mucilaginosa.

Toxicity.

Renal toxicity. In the LIN group there were significant more cases with a serum creatinine >1,3mg/dl before the start of VAN or LIN (VAN n=1, 1,7%, LIN n=4, 16%, p=0.026). But there was no statistical difference in the median GFR between both treatment groups (med. GFR VAN 98,15 ml/min, LIN 105,8 ml/min, p=0.638). During VAN or LIN application in both groups the serum creatinine level increased >0,5mg/dl in about 10% (VAN n=9, 15,3%, LIN n=2, 8%, p=0.493). Nephrotoxicity was also not significant different in the two treatment cohorts (grade 1 VAN n=5, 8,5%, LIN n=3, 12%, grade 2 n=0 in both groups and grade 3 VAN n=1, 1,7%, LIN n=0, p=0.707).

There were no significant differences in other potentially nephrotoxic medications during the treatment in both groups (liposomal amphotericin B or aminoglycoside therapy) (**Table 4**).

Liver toxicity. In one case of the VAN group, increased liver enzymes were detected (CTCAE grade 2), which decreased when the VAN application was stopped.

Haematologic toxicity. The patients treated with VAN showed a median duration of neutropenia of 18 days versus in the LIN treated patients, the median duration of neutropenia was 15 days, which was not significantly different (p=0.900).

Diarrhoea. 21 (42%) cases developed diarrhoea under treatment in the VAN group, vs 10 (43,5%) cases in the LIN group.

Only in the VAN cohorts drug levels were measured. The minimal VAN level was in the median of 1.95mg/dl (IQR1,0-3,5), and the maximum VAN level was in the median of 8 mg/dl (IQR 6,8-12,1). 50% of all measured VAN drug levels were in the therapeutic window (5-15mg/dl).

Cost analyses. The median duration of VAN therapy was 6 days when 7.5gr. VAN were applicated (IQR 4-12g); on the other side, LIN therapy was done in a median for 8 days, in which 8,4g LIN were given (IQR 6,3-12). Therefore, antibiotic therapy costs were significantly less in the VAN group (255,20 Euro) than in the LIN treated patients (1019,17 Euro).

Regarding all costs from the start of treatment with

VAN or LIN till the demission of the ward in the LIN group, there was a trend to lower costs than in the VAN group (LIN 13,349,76 Euro, VAN 15697,41 Euro, p=0.311).

Table 4. Renal function parameters.

	total n= 84	VAN n=59	LIN n=25	p
Creatinine elevated > 1.3mg/dl before antibiotic therapy start	5 (6 %)	1 (1.7 %)	4 (16 %)	0.026
Median GFR[1] before VAN/LIN-therapy (ml/min, IQR)	98 (79.30-131.10)	98.15 (80.00-131.25)	105.80 (65.80-131.10)	0.638
Median Minimal GFR during VAN/LIN-therapy (ml/min, IQR)	80.60 (61.70-107.50)	78.35 (63.20-105.20)	90.20 (55.40-111.05)	0.669
Median GFR at the end of antibiotic therapy(ml/min, IQR)	99.80 (80.90-137.20)	99.90 (81.12-135.20)	109.60 (73.60-141.50)	0.768
creatinine-elevation >0,5mg/dl n (%)	11 (13.1 %)	9 (15.3 %)	2 (8 %)	0.493
creatinine-elevation >1,3mg/dl during therapy	19 (22.6 %)	11 (18.6 %)	8 (32 %)	0.253
Nephrotoxicity				
- Grade 1	8 (9.5 %)	5 (8.5 %)	3 (12%)	0.690
- Grade 3	1 (1,2 %)	1 (1.7 %)	0 (0%)	1.000
Liposomal Amphothericin B- therapy n (%)	8 (9.5 %)	5 (8.5 %)	3 (12 %)	0.690
Duration Liposomal Amphotericin B- therapy (days, IQR)	6 (0-14)	2 (0-15)	13 (6-nr)	0.258
Aminoglycoside-therapy n (%)	7 (8.3 %)	7 (11.9 %)	0 (0 %)	0.098

[1]Glomerular Filtration-rate (Cockcroft-Gault), [2]NCI CTC Version 4.03.

Discussion. In current guidelines, VAN or LIN are recommended as an escalation regimen for fever in neutropenia when a gram-positive pathogen is suspected.

In our retrospective analysis, we tested the efficacy of these two different regimens (VAN vs LIN) and found no significant difference in the rate of defervescence with LIN or with VAN.

The finding that there is no significant difference in the efficacy in VAN or LIN was also reported by Jaksic et al. In their prospective multicentric randomised, double-blinded study, patients with haemato-oncologic diseases and proven gram-positive infections in neutropenia were randomised to treatment with LIN or VAN.[10] Treatment was done as 1st or 2nd line therapy. They could not find a significant difference in the efficacy (rate of defervescence) between the two treatment regimens.

Also, no difference in the efficacy of VAN vs LIN could be shown by Kohno et al.[11] They tested in a multicentre study VAN vs LIN in MRSA (methicillin-resistant Staphylococcus aureus) driven skin, mucosal infections, pneumonia and sepsis. However, these studies were not undertaken in patients with haematological malignancies or neutropenia in contrast to our cohort, and we had no MRSA infection in our group. Interestingly, the eradication rate at the end of antibiotic treatment was significantly higher in the LIN group.

In our analysis, bacteriaemia, pneumonia, and central venous catheter infections were the most detected foci for infection. Also, in the work of Jaksic et al.,[10] catheter infections and bacteriaemia were the most found infection sites in their neutropenic cohort. Interestingly, in a meta-analysis done by Falagas et al., empiric therapy with Lin vs glycopeptides or beta-lactam antibiotics LIN was significantly more effective in central venous catheters and bacteriemia.[11] In contrast to the study of Jaksic et al. with a low rate of pneumonia, pneumonia was more present in our cohort, with a significant accumulation in the LIN group (8-9% vs 27-60% in our cohort). This difference in the pneumonia rate in our data between the VAN and LIN treatment remains unclear.

In the data of Falagas et al. in pneumonia, there was no significant difference in the efficacy between LIN and glycopeptides.[11] However, in contrast, Kohno et al. could show that LIN had a significantly better efficacy on pneumonia.[12] Because of the relatively small patient group in our analysis, this could not be verified in our study, but eventually can help explain the trend to a better efficacy in the LIN group in our data.

In about half of the cases in our analysis, at least one bacterial pathogen could be detected, mainly gram-positive bacteria, and most of them were *Staphylococcus spp*. These findings are in line with Jaksic et al.[10] In their neutropenic patients' study, Staph were the most found bacteria, but in contrast to our patients, there was also relevant *Staph aureus* detected. In our cohort, only in the VAN group two gram-negative bacteria could be detected, but this was not significant, but could also be an explanation for the trend of lesser efficacy in the VAN group.

Mortality was not different between the two treatment groups in our analysis; this result was also found in the study of Jaksic et al.[10] Also, in a Cochrane analysis, no difference in mortality was described for VAN vs LIN.[13]

Another issue of both antibiotic regimens was the occurrence of toxicity. The already quoted study from Jaksic et al. reported significantly more side effects (like nausea, vomiting, flush and erythema) in the VAN group. However, the more frequent side effects did not lead to a

more often discontinuation in the VAN group.[10] In our analysis, we did not find a difference in the occurrence of nausea or vomiting in both groups, but it has to be kept in mind that our analysis was retrospective.

In the study of Jaksic,[10] there was no difference in the rate of diarrhoea in both groups, and this was also the case in our analysis. Nevertheless, interestingly in our study, the rate of diarrhoea was quite higher than in the study of Jaksic et al.. One reason could be the retrospective manner, which could make the evaluation of diarrhoea as a side effect of VAN or LIN difficult because there could be other reasons for diarrhoea in neutropenic patients after myelosuppressive chemotherapy. So this result has to be interpreted with caution.

Another known side effect of LIN is pancytopenia. However, in most cases, there has been a long-term treatment (more than 30 days) with LIN as a reason.[14] In line with this in our analysis (where the treatment with LIN had a median of seven days), we did not find a difference in haematological recovery between LIN and VAN. Also, Jaksic and coworkers and Nedved et al. could not find a difference.[10,15] In contrast, Kohno et al. could show that Lin was given for 10-28 days in case of pneumonia and skin infections, a higher incidence of anaemia and thrombocytopenia than the VAN group.[11]

Another issue is the potential nephrotoxicity of VAN. Our analysis did not find a significant difference in creatinine accelerations during VAN or LIN treatment. In contrast to our findings, Jaksic et al. could show significant more renal failures during VAN than LIN treatment.[10] These results were in line with Kohno et al., who showed significant renal impairment during VAN vs LIN therapy.[12] An explanation for the divergent results of our study could be the low vancomycin levels during VAN treatment. Only 50% of the VAN levels were in the therapeutic window. These sub-optimal levels could explain that we could not see a difference in renal toxicity between VAN and LIN, and it might also explain why the efficacy of treatment in the VAN group was lower than in the LIN group.

Also, Pritchard et al. established risk factors for VAN nephrotoxicity.[16] Beneath the risk of high VAN blood levels (10-15mg/dl), the VAN treatment was an important factor beyond seven days. In our analysis, the median VAN treatment time was 6 days, and the blood levels were mostly lower than 10mg/dl.

In our analysis, almost every second VAN treatment was stopped and switched to another antibiotic treatment because of fever persistence. In comparison to LIN, this was slightly not significant. There was no treatment discontinuation of VAN or LIN because of side effects, in contrast to the study of Jaksic et al. and Kohno et al., where both groups (VAN and LIN) had some treatment discontinuations because of side effects.[10,12] There was no significant difference between the VAN and LIN treatments in both studies.

Regarding the costs of the antibiotic therapy in our analysis, the LIN therapy was more expensive than the VAN therapy. However, we could detect a trend to a shorter hospitalisation time in the LIN group since treatment starts with LIN or VAN. A reason for the shorter hospitalisation time could be that the treatment was more often discontinued in the VAN group because of treatment failure and a new treatment had to be started, which needed again time for response. Therefore, due to the shorter hospital stay in the LIN group, all treatment with LIN was cheaper regarding the total hospital costs. In line with our findings are Patel et al.[17] Patel et al. compared the costs of VAN and LIN for treating MRSA nosocomial pneumonia, and they also found that the LIN treatment all in all was cheaper than treatment with VAN. As an explanation, they mentioned more complicated side effects during VAN treatment and a shorter hospitalisation time in the LIN group.

Conclusions. In our retrospective analysis of VAN or LIN treatment as escalation therapy in patients with hematologic malignancies, neutropenic fever and suggested gram-positive infection, the treatment with LIN showed a trend to a better defervescence. In addition, the time of hospitalisation was significantly shorter in the LIN group, which reduced the LIN group's costs even if the LIN medication was more expensive than the VAN medication. Nevertheless, it has to be kept in mind that our study was a retrospective analysis and that the case numbers were small. Because of these limitations, VAN may still be considered a reasonable option in patients with neutropenic fever, and randomised studies are needed in this field.

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