Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy

UNIVERSITÀ DEGLI STUDI DI TORINO

Infections by carbapenem-resistant *Klebiella pneumoniae* in stem cell transplant recipients: a nationwide retrospective survey from Italy

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Summary

Background. Infections by carbapenem-resistant *Klebsiella pneumoniae* (CRKp) may represent a challenging problem in stem cell transplant (SCT) recipients. However, little is known on their epidemiological and prognostic impact.

Methods. A retrospective survey (January 2010- July 2013) involving 52 Italian transplant centers was performed to assess the epidemiology of CRKp infections in autologous and allogeneic SCT and to analyze the factors associated to survival in patients with post-transplant CRKp infection.

Findings. Cases of CRKp infection were reported in 22% of autologous and in 61% of allogeneic SCT centers. CRKp infections were documented in 26 autologous and 87 allogeneic SCTs, with an incidence of 0.4% (from 0.1% in 2010 to 0.7% in 2013) and 2% (from 0.4% in 2010 to 2.9% in 2013) ,respectively. A CRKp colonization documented before or after transplant was followed by a post transplant infection in 27.9% of autologous and 28.8% of allogeneic SCT patients. The overall mortality rate was 16% in autologous and 70.1% in allogeneic SCT patients with CRKp infection. A CRKp infection documented before transplant (HR 0.33, 95% CI 0.15 – 0.74; p=0.007) and a not adequate first line antibiotic therapy (HR 2.67, 95% CI 1.43 – 4.99; p=0.002) were independent factors associated with an increased mortality in allogeneic SCT patients.

Interpretation. Our study shows dramatic findings of CRKp infections in SCT patients in Italy particularly after allogeneic SCT. The detection of carriers to implement isolation measures, and the definition of early, active therapeutic strategies represent critical aspects of the management of CRKp infections after SCT.

Introduction

The increasing incidence of infections by carbapenem resistant *Klebsiella pneumoniae* (CRKp) is a significant public health challenge worldwide (1,2). CRKp isolates have caused numerous infection outbreaks in United States, Israel, Greece, China and South America, and an increasing epidemiological impact has also been observed in Italy in the last few years (1-7).
Infections caused by CRKp isolates are associated with high morbidity and mortality rates particularly in high risk intensive care unit (ICU) and solid organ transplant (SOT) patients (8-14). Infection and colonization by these multiresistant bacteria may represent a challenging problem in stem cell transplant (SCT) recipients not only for the management of post-transplant complications but also for the eligibility to transplant itself when patients acquire the pathogen before the transplant procedure (15,16). However, little is known on the overall epidemiological and prognostic impact of these infections in the autologous and allogeneic SCT population.

To assess the current epidemiology, clinical characteristics and outcome of CRKp colonization and infection in SCT patients, the Gruppo Italiano Trapianto Midollo Osseo (GITMO) retrospectively collected data of patients undergoing allogeneic and autologous SCT during the period 2010-2013. These data provide the basis for promoting direct efforts in the management of CRKp infections in the SCT population.

Patients and methods

The retrospective survey involved 52 transplant centers in Italy to assess the incidence of colonization and infection by CRKp isolates before and after SCT. Enrollment was limited to patients undergoing autologous or allogenic SCT during the period from January 2010 through July 2013. Cases of CRKp infection or colonization documented in patients who relapsed and were submitted to further chemotherapy after SCT were not considered.

Data collection. Each transplantation centre completed a questionnaire reporting the number of allogeneic and autologous SCTs performed during the period of study at each centre, and the following data regarding patients with CRKp colonization or infection documented during the 3 months before transplant and during the first year after transplant or until December 2013 when the data collection was frozen: patient's demographic characteristics, diagnosis and phase of the underlying disease, stem cell donor, pretransplant conditioning regimen and timing of colonization and/or infection before and after SCT. Information pertaining to the cases of CRKp infection included also time of onset of infection after transplant, site of infection, development of septic shock, details on first line and second line antibiotic therapy, survival at 3 months from infection and cause of death. First line antibiotic therapy was defined as the treatment administered at the onset of the febrile/infectious episode regardless of the following microbiological CRKp infection documentation. Any subsequent modification of the treatment, empirical or based on microbiological evidence, was considered a second line antibiotic therapy.

Definitions. The following terms were defined prior to data collection and analysis. A CRKp colonization was defined as the isolation of the microorganism from any non sterile body site (usually respiratory tract/oral cavity, rectum, vagina, skin and urine) in absence of clinical findings suggestive of an infection. A proven CRKp infection was defined as the isolation of the microorganism from blood-cultures (at least 1 specimen) or other usually sterile body sites in association with clinical signs of the systemic inflammatory response syndrome (17). A probable CRKp infection was defined as the isolation of the microorganism from a non sterile body site (in particular respiratory and urinary tract) in presence of clinical signs of infection and of systemic inflammatory response syndrome, and after the exclusion of other possibly involved etiologies. Onset of CRKp infection was defined as the date of collection of the first positive culture for proven cases or of the clinical documentation of the deep infection for probable cases. Septic shock was defined as sepsis associated with organ dysfunction and persistent hypotension despite volume replacement (17).

Microbiology and antibiotic therapy. Each center was requested to report all cases of colonization and infection by *K. pneumoniae* that exhibited minimum inhibitory concentrations (MICs) for imipenem and/or meropenem and/or ertapenem higher than 1 mg/L documented in the 3 months before and until one year after transplant. Identification and susceptibility testing of the CRKp isolates were performed according to the local microbiologic methods used at each laboratory but no specific information was requested. We considered an adequate antibiotic therapy an association including at least two of colistin, tigecycline and gentamicin, with at least one of them active in vitro against the isolate (9).

Ethical statement. This study was approved by the GITMO Review Board and informed consent for the use of clinical data for scientific purposes was obtained from all patients receiving SCT whose clinical data are regularly admitted in the GITMO databases. This was a non-interventional, retrospective, cohort study and the collection and storage of data were performed by the investigators directly involved in the patients' care using current techniques of ensuring privacy; ethics committee approval was not, therefore, necessary.

Analyses. The aim of our study was to describe the incidence of colonization and infection by CRKp isolates documented before (3 months) and after (up to 12 months) SCT and the overall survival (OS) at 3 months of CRKp infections documented after SCT. Mortality attributable to CRKp infection was defined as death occurred in patients who failed to respond to therapy and in patients with a partial response to therapy who died as the result of an acute event involving any of the sites of infection or of an unknown cause. OS was calculated from the documentation of a CRKp infection to the date of death or last follow-up. The outcome for survival was truncated at a 3-months period of follow-up. Variables considered in the analysis of OS were: age (≤median years vs >median years), gender (male vs female),underlying disease (acute leukemia vs other diseases), phase of the underlying disease (remission or stable chronic vs active disease), type of donor for allogeneic SCT (matched family vs haploidentical or unreleted volunteer or cord blood), conditioning regimen for allogeneic SCT (myeloablative vs non myeloablative of reduced

intensity), CRKp colonization before transplant (no vs yes), CRKp infections before transplant (no vs yes), level of CRKp infection documentation (proven vs probable), first line antibiotic therapy (adequate vs non adequate). The probability of survival was calculated using the Kaplan-Meier estimate and a Kaplan Meier curve was generated to illustrate OS. Univariate and multivariate Cox regression analyses were performed to evaluate the impact of the above variables on 3 month survival of the patients who developed CRKp infection after transplant. Variables that reached a P-value of .20 after univariate analysis were included in the initial models and variables were eliminated one at a time in a stepwise fashion to only keep variables that reached a P value of .05 or less into the final models. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were determined, and P values were calculated using the likelihood ratio test. Descriptive statistics included absolute and relative frequencies for categorical data, and median, mean and range for numerical measurements. The analyses were performed using SPSS software for Windows, version 17.0.

Results

Overall 6058 patients from 49 transplant centers and 4389 patients from 46 transplant centers received autologous and allogeneic SCT, respectively. They accounted for 54% of autologous SCTs and 72% of allogeneic SCTs performed in Italy during the study period (January 2010 – July 2013) (www.gitmo.org).

Isolation of CRKp (colonization or infection) after transplant was reported in 15 of 49 (30.6%) autologous SCT centers and in 29 of 46 (63.0%) allogeneic SCT centers. In particular, 11 of 49 (22.4%) autologous SCT centers and 28 of 46 (60.9%) allogeneic SCT centers documented at least one case of CRKp infection after transplant. There was no difference in the epidemiological distribution of CRKp in the transplant centers of north, middle and south of Italy.

The data on CRKp colonization and infection documented before and after SCT over the years are detailed in Table 1. Overall, 26 and 87 cases of CRKp infection were reported 8 ($\pm$11.6 days) median days from autologous and 15 ($\pm$ 83.6 days) median days from allogeneic SCT,

respectively. The incidence of CRKp infections was 0.4% (from 0.1% in 2010 to 0.7% in 2013) in autologous and 2% (from 0.4% in 2010 to 2.9% in 2013) in allogeneic SCT populations (Figure 1). Considering only the centers in which at least one CRKp infection was documented, the incidence was 1.2% (range 0.2 to 5%) and 2.6% (range 0.5 to 15.2%) of patients in autologous and allogeneic SCT centers, respectively. The incidence of CRKp infections in children (age ≤ 18 years) was 0.3% (1 of 376 transplants) in autologous SCT and 1.8% (15 of 820 transplants) in allogeneic SCT. The characteristics of post-transplant CRKp infection cases are detailed in table 2.

The correlation between post transplant CRKp infections and previous CRKp isolation is detailed in table 3. Overall, out of 43 autologous SCT and 73 allogeneic SCT patients with a CRKp colonization documented before or after transplant, 12 (27.9%) and 21 (28.8%) developed an infection, respectively. Recurrence of infection after transplant occurred in 1 of 3 (33.3%) and 10 of 22 (45.4%) autologous and allogeneic SCT patients with an infection documented before transplant, respectively.

The overall mortality rate at 3 months from the diagnosis of CRKp infection was 16% (4 of 25 patients) in autologous SCT patients and 70.1% (61 of 87 patients) in allogeneic SCT patients (Figure 2). The mortality rate in children (age ≤ 18 years) submitted to allogeneic SCT was 60% (9 of 15 patients). The CRKp infection was considered the primary cause of death in all autologous SCT patients and in 56 (91.8%) allogeneic SCT patients who died, with an attributable mortality rate of 16% and 64.4%, respectively. Out of 6 autologous and 43 allogeneic SCT patients who developed septic shock ,3 (50%) and 38 (88.4%) died due to the CRKp infection, respectively.

In multivariate analysis, a CRKp infection documented before transplant (HR 0.33, 95% CI 0.15 – 0.74; p=0.007) and a not adequate first line antibiotic therapy (HR 2.67, 95% CI 1.43 – 4.99; p=0.002) were independent factors associated with mortality. Also an active hematologic disease at transplant and an older age were associated to a poorer outcome, although not significantly (Table 3). No survival variable was statistically significant for autologous SCT in univariate analysis (data not shown).

Discussion

The increasing resistance to carbapenems among *K.pneumoniae* has become a public health problem of major concern worldwide (1-3). In Europe, until 2009, the proportion of CRKp has remained overall low in most countries except Greece and Cyprus, where high-level endemicity has been reported since the mid-2000s (18). In Italy, sporadic cases or outbreaks caused by CRKp have been reported since the early 2000s, but only since 2010 an abrupt and notable increase in the proportion of CRKp has been observed by the EARS-NET surveillance system (18), and shown to be mostly caused by the dissemination of strains producing KPC-type carbapenemases (7). Most of the case series of CRKp infections relate to ICU and SOT patients (9-14). SCT patients have been considered at risk for these severe infections too, but only few information is specifically available regarding the incidence and prognostic factors in this population of immunocompromised subjects (15,16).

In consideration of the emerging morbidity and mortality for CRKp infections reported by some SCT Italian centers , the GITMO decided to investigate the phenomenon at national level with the aim to know the geographic epidemiology and the overall clinical and prognostic impact of this emerging complication in the autologous and allogeneic SCT populations. A prospective survey of severe gram negative infections involving most of GITMO transplant centers is ongoing (Clinicaltrials.GOV….), but the rapidly growing epidemiological impact of CRKp infections prompted the GITMO to perform a retrospective study focused on CRKp colonization and infection in the SCT Italian population in order to obtain any information to clarify the epidemiological patterns and to early plan shared, tailored infection control strategies. The retrospective collection of the data and the lack of some microbiological information (i.e. molecular characterization of the isolates) are important limits of this study but the involvement of a large, representative number of centers and the considerable number of CRKp infections reported represent a valuable characteristic of the survey.

As expected, there was a significantly different epidemiology of CRKp in the autologous and allogeneic SCT populations. Although an increasing trend of infections was observed also in autologous SCT patients since 2010, the epidemiological impact of CRKp in this type of transplant seems to be quite favorable not only for the limited geographical spread (22% of autologous SCT centers from 6 regions reported at least 1 case of CRKp post-transplant infection) and the low overall incidence of the infection (0.4%), but also for the contained mortality rate (16%). The type of the underlying disease, mainly represented by chronic lymphoprolipherative malignancies, and of the chemotherapy treatment before transplant usually administered in an outpatient setting and the short period of post-transplant neutropenia probably represent the reasons for the favorable epidemiology of CRKp in the autologous SCT population.

Indeed, the dramatic findings observed in allogeneic SCT deserve a careful analysis. In line with the national data reported by the EARS-NET surveillance system (18), a significant increase of cases of CRKp infection was observed in the last few years (from 0.4% in 2010 to 2.9% in 2013), and 60% of allogeneic transplant centers from 14 of the 20 italian regions documented at least one case of CRKp infection. Furthermore, the incidence reported for the transplants performed in 2013 may be underestimated considering the shorter follow-up period as compared to the previous years. Outbreaks involving a large proportion of patients (reaching 15% of transplants in one center) occurred in some centers with a significant impact in the transplant related mortality rate.

The most relevant data of our survey was represented by the infection-related mortality (64.4%) observed in allogeneic SCT patients, comparable or higher than that reported in previous series of ICU (32-41%) and SOT (0-71%) patients (9-14). The analysis of the variables of survival demonstrated the independent impact of the history of an infection documented prior to transplant and of the adequacy of the first line antimicrobial therapy in the outcome of the patients. Retrospective studies in ICU patients have examined mortality in relation to antibiotic treatment for CRKp bloodstream infections and demonstrated that the use of combinations with appropriate

antibiotics are associated with increased survival. Tumbarello and colleagues, while reporting a crude 30-day mortality of 42% in 125 bloodstream infections due to CRKp, demonstrated that only the triple combination of colistin, tigecycline, and meropenem was associated with increased survival as compared to other treatments (9). Similarly, in the study by Zarkotou and colleagues, which included 53 bloodstream infections caused by CRKp, all patients who received appropriate combination treatment survived whereas patients treated with monotherapy—including colistin monotherapy— experienced a high infection-attributable mortality (47%) (10). In a further study, Qureshi and colleagues reported crude 28 day mortality of 13% and 58% among patients treated with active combination and monotherapy, respectively (19).

In our cases, an association of at least two of colistin, tigecycline and gentamicin (with at least one antibiotic active in vitro against the isolate) was administered in 31 (35.6%) allogeneic SCT patients since the first day of fever or at the onset of other clinical signs before the microbiological documentation of the CRKp infection. The use of a first line CRKp active treatment, which is not considered a standard empiric antibiotic therapy in hematologic patients, was driven by the documentation of a prior CRKp colonization or infection, or by the local epidemiology in some centers with an ongoing outbreak. In these patients the infection related mortality rate was 48% as compared to 73% in patients who received a not active first line antibiotic therapy. It was not possible to compare the efficacy of the different active antibiotic associations (see table 2) due to the limited number of cases. The recently published guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4) on targeted therapy against multiresistant bacteria in leukemic and SCT recipients underline the need of the above non-conventional agents as a treatment option of CRKp infections (20). The use of these associations should be based on in vitro susceptibility data, and a careful assessment of the risk-benefit balance (20). However, our data seem to suggest that an early risk and epidemiology-driven antimicrobial strategy in the allogeneic SCT population may be required. In view of the short median time of death (5 days) from the onset of the infection, a strategy leading to a tailored antibiotic treatment before the documentation of CRKp infection may

be considered. On the other hand, the outcome of patients who received a first line active antibiotic therapy continued to be very poor. In particular, 9 of 10 (90%) patients with a CRKp infection documented before transplant and who developed a recurrence of the infection after transplant early died despite an active antibiotic therapy.

A predictive significance of colonization in the development of a CRKp infection was shown in our study in which nearly one-third of patients with a CRKp colonization, documented before or after transplant, developed an infection. On the other hand, in a large number of patients with a post-transplant infection no previous colonization was reported. The difficulties in the detection of colonization may justify this finding, however, the lack of a well-defined colonization survey strategy in several centers was probably the cause of an under-documentation of a CRKp colonization preceding the infection. This is a crucial point of the CRKp infection control strategy if we consider the importance of the knowledge of the colonization by multiresistant microorganisms in tailoring an early, active antibiotic therapy.

In conclusion, our study shows dramatic findings of CRKp infections in allogeneic SCT patients. The lack of treatments active against this multiresistant pathogen represents a challenging issue also considering the paucity of new antibacterial drugs in the near future (20,21).The poor outcome observed also in patients who received a presumably effective first line antibiotic therapy makes it a priority to prevent infections with control measures. The detection of the carriers to implement isolation measures avoiding nosocomial transmission, and to define an early tailored therapeutic strategy represents a critical aspect of the management of CRKp infections in the SCT population (22-25).

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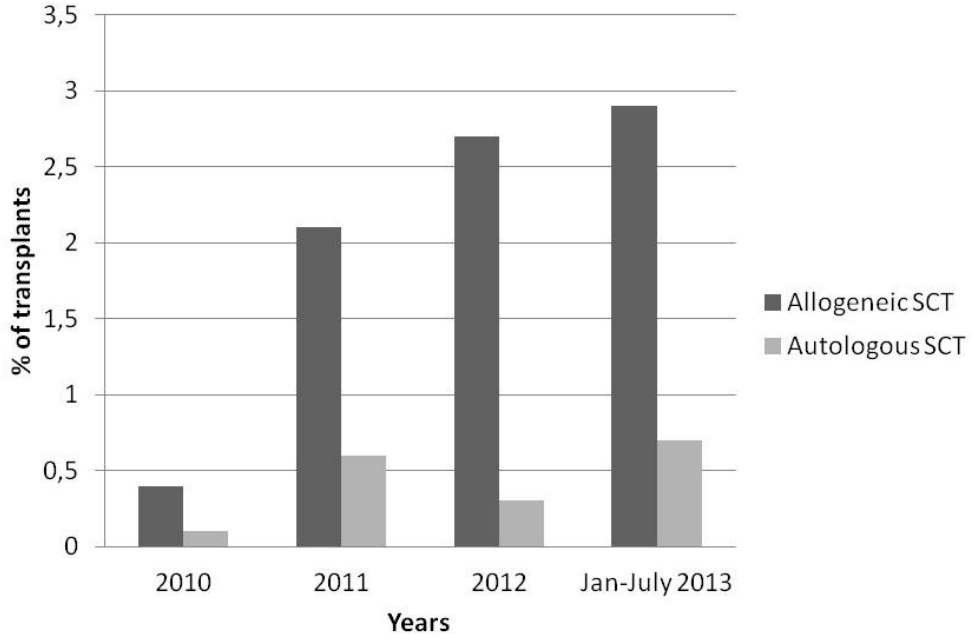
Figure 1. Incidence of post-transplant CRKp infections in autologous and allogeneic SCT patients.



Incidence in 2013 possibly underestimated due to the shorter post-transplant follow-up period as compared to the previous years

Figure 2. Overall survival of patients with CRKp infection documented after allogeneic SCT

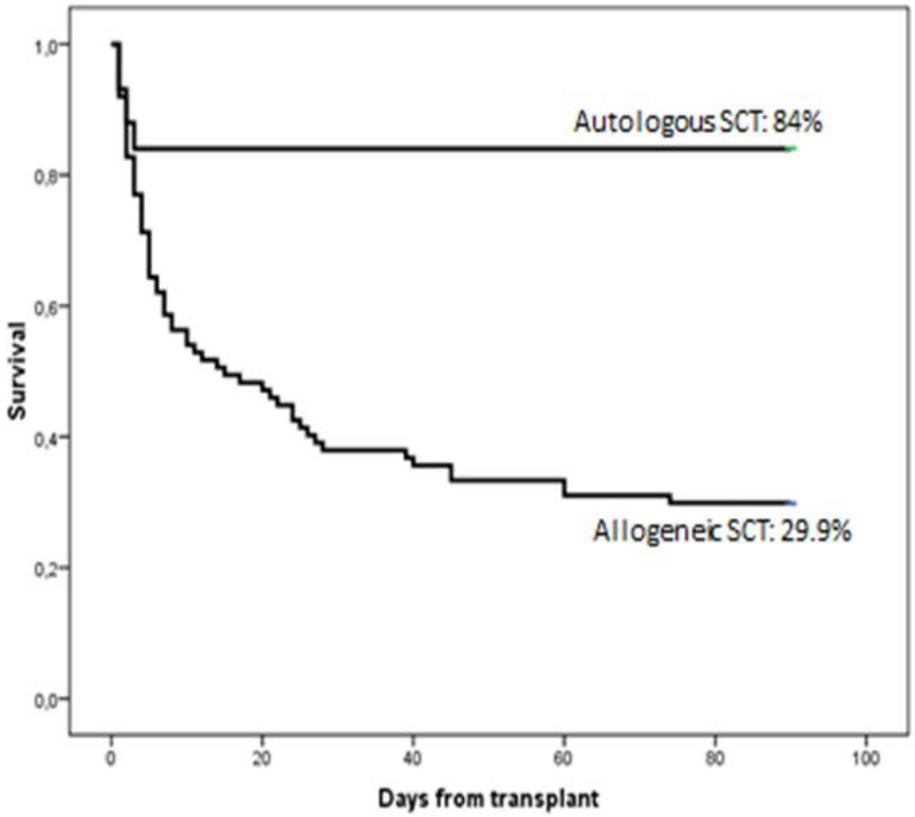


Table 1. Cases of colonization and infection by CRKp isolates documented in the 3 months before and in the 12 months after autologous and allogeneic SCT

	Autologous SCT				
	2010 (1603 SCT)	2011 (1673 SCT)	2012 (1678 SCT)	Jan-July 2013^ (1104 SCT)	Total (6058 SCT)
Colonization before SCT, n. of cases (% of SCT)	0 (0)	1(<0.1)	5 (0.3)	7 (0.6)	13 (0.2)
Infection before SCT, n. of cases (% of SCT)	0 (0)	1 (<0.1)	0 (0)	2 (0.2)	3 (<0.1)
Colonization after SCT#, n. of cases (% of SCT)	6 (0.4)	5 (0.3)	8 (0.5)	11 (1.0)	30 (0.5)
Infection after SCT*, n. of cases (% of SCT)	2(0.1)	10 (0.6)	5 (0.3)	8 (0.7)	25 (0.4)
Centers with at least one case of infection after SCT, n. (% of 49 centers)	1(2)	7 (14.3)	4(8.2)	5(10.2)	11(22.4)
	Allogeneic SCT				
	2010 (1139 SCT)	2011 (1221 SCT)	2012 (1261 SCT)	Jan-July 2013^ (768 SCT)	Total (4389 SCT)
Colonization before SCT, n. of cases (% of SCT)	0 (0)	10 (0.8)	13 (1)	9 (1.2)	32 (0.7)
Infection before SCT, n. of cases (% of SCT)	0 (0)	3 (0.2)	11 (0.9)	8 (1.0)	22 (0.5)
Colonization after SCT#, n. of cases (% of SCT)	1 (<0.1)	7 (0.6)	16 (1.3)	17 (2.2)	41 (0.9)
Infection after SCT*, n. of cases (% of SCT)	5 (0.4)	26 (2.1)	34 (2.7)	22 (2.9)	87 (2.0)
Centers with at least one case of infection after SCT, n. (% of 46 centers)	3(6.5)	16 (34.8)	15 (32.6)	16 (34.8)	28 (60.9)

Patients with colonization or infection documented before transplant excluded

* In allogeneic SCT, the incidence of CRKp infections (p=0.0004) and the rate of centers with at least one documented case (p=0.001) significantly increased from 2010 to 2011. In autologous SCT, the incidence of CRKp infections increased not significantly in the years while the rate of centers with at least one documented case significantly increased from 2010 to 2011 (p=0.03).

^ Incidence in 2013 possibly underestimated due to the shorter post-transplant follow-up period as compared to the previous years

Table 2. Characteristics of patients with CRKp infection documented after autologous and allogeneic SCT.

	Autologous SCT (25 cases)	Allogeneic SCT (87 cases)
Male sex, n. (%)	17 (68)	50 (57)
Age, years, median ± SD	55 ± 14.6	43 ± 17.9
Children , ≤ 18 years, n. (%)	1 (4)	15 (17.2)
Underlying disease, n. of cases (%)		
Acute myeloid leukemia	2 (8.0)	38 (43.7)
Acute lymphoid leukemia	0	18 (20.7)
Non Hodgkin lymphoma	13 (52.0)	11 (12.6)
Hodgkin lymphoma	2 (8.0)	0
Multiple myeloma	7 (28.0)	1 (1.1)
Myelodisplastic syndrome	0	6 (6.9)
Chronc myeloprolipherative disease	0	7 (8.0)
Aplastic anemia	0	4 (4.6)
Other	1 (4.0)	2 (2.3)
Phase of the underlying disease, n. of cases %		
I complete remission	7 (28.0)	28 (32.2)
≥II complete remission	10 (40.0)	19 (21.8)
Partial remission, chronic disease	5 (20.0)	12 (13.8)
Active disease	3 (12.0)	28 (32.2)
Type of donor, n. of cases (%)		
Matched related	NA	29 (33.3)
Haploidentical		10 (11.5)
Unrelated volunteer		41 (47.1)
Cord blood		7 (8.0)
Type of conditioning regimen, n. of cases (%)		
Myeloablative	25 (100)	49 (56.3)
Non myeloablative-Reduced intensity	/	38 (43.7)
Time of onset from SCT, median days ± SD	8 ± 11.6	15 ± 83.6
Level of CRKp infection documentation, n. of cases (%)		
Proven	23	77
Probable*	2	10
Site of infection		
Blood only	22	54
Blood plus lung	1	11
Blood plus skin	0	3
Bloos plus gut	0	8
Skin	0	1
Lung only	2	10
Septic shock	6 (24)	43 (49.4)
Adequate first line antibiotic therapy@	6 (24)	31 (35.6)
Tigecycline – gentamicin (+- meropenem)	0	11
Colistin – gentamicin (+- meropenem)	2	11
Colistin – tigecycline – gentamicin (+-meropenem)	1	2
Colistin- Tigecycline – (+- meropenem)	3	7
Overall mortality at 3 months, no of cases (%)	4 (16)	61 (70.1)
Deaths attributed to CRKp infection, n. of cases (%)	4 (100)	56 (91.8)

NA: not applicable; # after engraftment in 35 cases (40%)

*all cases of pulmonary infiltrate with CRKp isolation from respiratory tract and no evidence of other pathogens.
@ First line antibiotic therapy was considered adequate if included at least two of colistin, tigecycline and gentamicin, with at least one drug in vitro active against the isolate

Table 3. Correlation between CRKp post transplant infections and previous CRKp isolation

Type ant timing of CRKp isolation	No. of post transplant infections /no. of pts with previous isolation (%)	
	Autologous SCT	Allogeneic SCT
Colonization before transplant	3/13(23.1)	10/32 (31.2)
Infection before transplant	1/3 (33.3)	10/22 (45.4)
Colonization after transplant	9/30 (30)	10/41 (24.4)

Table 4. Probability of Overall Survival at 3 months from CRKp infection in 87 allogeneic SCT patients

	OS, %	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Male vs Female	28 vs 32	1.04 (0.62-1.73)	0.88		
Age , ≤ 43 years vs > 43 years	37 vs 22	0.67 (0.40-1.10)	0.11	0.59 (0.34-1.01)	0.056
Underlying disease, acute leukemia vs other	27 vs 35	1.30 (1.30-0.76)	0.33		
Status of the underlying disease at transplant, Complete remission/stable vs active	36 vs 18	0.56 (0.33-0.44)	0.03	0.61 (0.35 – 1.06)	0.080
CRKp colonization before transplant, No vs yes * @	30 vs 50	1.76 (0.70-4.43)	0.23		
CRKp infection before transplant, No vs yes *	32 vs 10	0.51 (0.25-1.04)	0.06	0.33 (0.15 – 0.74)	0.007
Myeloablative conditioning yes vs no	29 vs 32	1.22 (0.74-2.03)	0.44		
Donor type Matched related vs mismatched related or unrelated volunteer donor or cord blood	31 vs 28	0.95 (0.56-1.61)	0.85		
Level of CRKp infection documentation, proven vs probable	31 vs 20	0.89 (0.42-1.87)	0.76		
First line antibiotic therapy, Not adequate vs adequate	21 vs 45	1.76 (1.05-3.10)	0.04	2.67 (1.43 – 4.99)	0.002

*During the 3 months preceding SCT

@Ten patients with a previous CRKp infection excluded.