REVIEWS

Autologous stem cell transplantation in Kuwait cancer control centre: Review of infections in the first thirty days post-transplant

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Received: April 15, 2012 **Accepted:** May 20, 2012 **Published:** June 1, 2012
DOI: 10.5430/jhm.v2n2p39 **URL:** http://dx.doi.org/10.5430/jhm.v2n2p39

Abstract

Autologous peripheral blood stem cells (PBSC) following high-dose chemotherapy is established in Kuwait Cancer Control Center since 2000. We studied the incidence of microbial infections during the first 30 days following autologous PBSC transplantation in 120 consecutive patients with non-Hodgkin's lymphomas, Hodgkin's lymphoma, multiple myeloma, and acute myeloid leukemia. The incidence and consequences of these infections are reported. All the patients received antibiotic prophylaxis and hematopoietic growth factors during neutropenia. The mean duration of severe neutropenia was 7 days (Range 5-9) in all the patients, and the median time to myeloid engraftment was 11 days. The incidence of culture-proven infections in non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma patients was similar. Infections could be documented clinically only in 67 patients (72.8%) where they had culture-negative infections. In 25 patients clinical infection was supported by positive cultures. The isolated organisms included Gram-negative organisms in 56%, Gram positive in 24%, and both Gram negative and Gram positive in 16% of the patients. In 4% of the patients fungi were isolated. The most common sites of infections were central line (catheter) infection (68%). Among central line infections, isolates were Gram positive in 35.3%, Gram negative in 41.2%, both Gram negative and Gram positive in one patient and fungi in one patient. Although the overall incidence of infections among autologous SCT recipients is modest, because patients tended to have rapid recovery of their immune system, infections remain a significant cause of morbidity stressing the importance of prevention and management of infectious diseases.

Key words

Autologous stem cell transplant, Infections, Kuwait

Introduction

Autologous Stem Cell Transplantation in Kuwait has been performed since 2000. The program serves all the population of Kuwait. In 2009, the estimated population of Kuwait was 3.5 million, including 1.1 million (31.4%) Kuwaitis and 2.4 million (68.6%) non-Kuwaitis [1]. Expatriates and their family's resident in Kuwait have an equal chance, like Kuwaitis, to receive Autologous Stem Cell Transplantation in the Kuwait Cancer Control Center (KCCC).

High-dose chemotherapy with autologous peripheral blood stem cell (PBSC) or bone marrow (BM) transplantation has become accepted consolidation or salvage therapy for various hematologic malignancies in patients aged ≤ 65 years [1, 2].This approach is associated with improved response rates, overall survival, and event- free survival compared to conventional chemotherapy. A number of non-randomized [3-6], randomized [7-9] and population-based studies [10] as well as two recent meta-analyses have supported these observations [11, 12]. Infections remain a significant cause of morbidity in this brief post-transplant neutropenia, despite rapid hematopoietic reconstitution with the use of mobilized autologous peripheral blood stem cell grafts, the use of hematopoietic growth factors after transplant, antibacterial, antiviral and antifungal prophylaxis as well as the transfusion support which reduced morbidity and mortality by shortening post-transplant neutropenia and its attendant complications [13-15].

We have analyzed the microbial etiology of infections in 120 consecutive patients with Non-Hodgkin's and Hodgkin's lymphoma and multiple myelomas who received high dose chemotherapy and autologous stem cell transplant. We reviewed all episodes of infections occurring in first 30 days following autologous PBSC transplantation. The frequency, pattern of microbial infections, and consequences of these infections reflected on the transplant related mortality are reported.

Patients and methods

Between January 2000 and November 2010, 120 patients with non-Hodgkin's and Hodgkin's lymphoma, multiple myeloma, few cases of acute myeloid leukemia and one case of testicular seminoma received high dose chemotherapy and underwent autologous peripheral blood stem cell transplantation. Patients have given consent to use the clinical information contained in their treatment records for clinical analysis and publications for scientific communities. Nationalities of the patients were reported because ethnic, sociocultural, and economic factors have a significant impact on different aspects of cancer care including prevention, screening and early detection, treatment, enrollment in clinical trials, survivorship, palliative care, and end-of-life care [16, 17]. In addition to these factors, expatriates are exposed to expatriation-related stressors [18, 19]. Patient characteristics are shown in Table 1. There were 12 Kuwaiti male patients (54.5%) with mean age 36.72 ± 10.98 years (Range, 16-54) and 10 (45.5%) females, with mean age 43.22 ± 14.95 years (Range, 20-60). Within the Non-Kuwaiti group there were 69 (70.4%) males, with mean age 38.24 ± 11.91 years (Age range 15-58) and 29 (29.6%) females, with mean age 32.61 ± 15.65 years (Range 12-61). Among the Non-Kuwaiti patients there were 65 (66.3%) Non-Kuwaiti Arab and other nationalities were 33 (33.7%). Among the Non-Kuwaiti Arab the most common nationality was Egyptians 33 (33.7%) patients followed by 8 Syrians patients (8.2%). Among the Non-Kuwaiti other nationalities the most common nationality was Indians 21 patients (21.4%) and followed by 7 Bengalis patients (7.1%).

Table 1. Characteristics of patients undergoing autologous stem cell transplantation

No.	**120**
Median age (Range) years	42 (12-61)
Sex	
Male	81 (67.5%)
Female	39 (32.5%)
Nationality	
Kuwaiti	22 (18.3%)
Non-Kuwaiti	98 (81.7%)
Diagnosis	
Group 1	
Non-Hodgkin's lymphoma	45 (37.5%)
Low-grade non-Hodgkin's lymphoma	26 (57.7%)
Diffuse large B-cell lymphoma	19 (42.3%)
Group 2	
Hodgkin's disease	36 (30%)
Group 3	
Multiple myeloma	33 (27.5%)

Shown are number (%) of patients with specific characteristics.

The age at autologous stem cell transplantation in the three groups is shown in table 2

Table 2. Age at autologous stem cell transplantation

Diagnosis		Nationality	Age at transplant				
			Mean	Median	Sd	Min	Max
Non-Hodgkin's lymphoma	Low-grade	Kuwaiti	51.86	53	8.71	34	60
		Non-Kuwaiti	45.06	48.5	11.12	24	61
	Diffuse large B-cell	Kuwaiti	38	36	5.29	34	44
		Non-Kuwait	38.08	37	13.53	14	58
Hodgkin's lymphoma		Kuwaiti	33.43	29	13.93	16	54
		Non-Kuwait	29.57	28	10.98	12	52
Multiple Myeloma		Kuwaiti	47.33	48	3.06	44	50
		Non-Kuwait	47.4	48	6.98	34	57

Patients' status at transplant is shown in table 3

Table 3. Status at autologous stem cell transplantation

Diagnosis		Pre-transplant chemotherapy & No. of patients		No. of patients (%)	Status at transplant	
					No of patients (%) complete response	No of patients (%) partial response
Non-Hodgkin's lymphoma	Low-grade	DHAP ± R	14			
		DHAP + MINE + ESHAP	1			
		ICE	3	26 (21.7)	24 (92.3)	2 (7.7)
		MINE	3			
		CHOP ± R	5			
	Diffuse large B-cell	ESHAP ± R	11			
		ESHAP + ICE	3	19 (15.8)	16 (84.2)	3(15.8)
		HyperCVAD	5			
Hodgkin's lymphoma		COPP	1			
		MINE	1			
		ESHAP + Radiotherapy	1			
		Gemzar + Caleyx + Dexamethasone	2	36 (30.1)	31 (86.1)	5 (13.9)
		DHAP	8			
		ICE	23			
Multiple myeloma		VAD	9			
		CTDa	22	33 (27.2)	autologous stem cell transplantation as primary consolidation	
		VTD	2			

Acute myeloid leukemia patients (4.2%) five in CR2 & CR3 and one Cancer testis patient (0.8%) in CR3. These patients were not included in the analysis because of their small number.

The salvage chemotherapy used in 45 (36.7%) Non-Hodgkin's lymphoma patients was DHAP ± R [Cisplatin 100mg/m^2 day 1, cytarabine 4 (2g/12h) g/m^2 day 2, dexamethasone 40mg/day days 1-4, with or without Rituximab 375mg/m^2] in 14 cases, DHAP was followed by MINE [Mesna and ifosfamide 1330mg/m^2 and etoposide 65mg/m^2 i.v. days 1-3, and mitoxantrone 8mg/m^2 i.v. day 1) then ESHAP (Etoposide 40mg/m^2/day IV Day 1, 2, 3 and 4, Solumedrol 500mg/m^2/day IV Day 1, 2, 3, 4 and 5, Cytarabine 2Gm/m^2/day IV Day 5 -To start immediately after Cisplatin completed, Cisplatin 25mg/m^2/day IV Day 1, 2, 3 and 4; Given as a continuous infusion over 24 hours] in 1 case, ESHAP ± R in 11 cases, in one of them ESHAP was followed by radiotherapy, ESHAP was followed by ICE {Ifosfamide 5000mg/m^2 intravenously (i.v.) fractionated into three equally divided doses over 3 days, carboplatin [mg dose = 5 x area under the curve (AUC)] i.v. on day 1 and etoposide 100mg/m^2 i.v. daily for 3 days} in 3 cases, ICE was used in 3 cases, MINE (Mesna and ifosfamide

1330mg/m^2 and etoposide 65mg/m^2 i.v. days 1-3, and mitoxantrone 8mg/m^2 i.v. day 1) was used in 3 cases, Hyper CVAD {Hyper fractionated cyclophosphamide 300mg/m^2 b.i.d. i.v. (3 h infusion) day 1-3 with mesna uroprotection, vincristine 1.4mg/m^2 (Max 2mg) i.v. day 4+11 (12 h after cyclophosphamide), doxorubicin 16.7mg/m^2 day 4-6, and dexamethasone 40 mg i.v. or p.o. day 1-4, 11-14, with growth factor support. Rituximab 375mg/m^2 i.v. day 0, alternated with courses of high-dose methotrexate 200mg/m^2 i.v. (2 h infusion) day 1 followed by 800mg/m^2 i.v. Continuous infusion with folinic acid rescue, and cytarabine 3000mg/m^2 b.i.d. i.v. (2 h infusion) day 2+3} in 5 cases, and CHOP ± R [Cyclophosphamide (Cytoxan) 750mg/m^2 day 1, doxorubicin (Adriamycin) 50mg/m^2 day 1, vincristine (Oncovin) 1.4mg/m^2 (Max 2mg) i.v. day 1and prednisone 100mg/day p.o. days 1-5 ± rituximab 375mg/m^2 i.v. day 1] in 5 cases. The salvage chemotherapy used in 36 (30%) Hodgkin's lymphoma cases was COPP [Cyclophosphamide 500mg/m^2 i.v. day 1+8, Vincristine 1.4mg/m^2 (Max 2mg) i.v. day 1+8, Prednisone 40 mg/m^2 p.o. (3 doses) day 1-14, Procarbazine 100mg/m^2 (Max 150mg) p.o. (2-3 doses) day 1-14] in 1 case, MINE in 1 case, ESHAP followed by radiotherapy 36 Gy in 1 case, Gemzar 1000mg/m^2, Navelbine 20mg/m^2, & Caelyx 15mg/m^2 Gemzar, Navelbine, & Caelyx were given day 1 and day 8 every 21 days in 2 cases, DHAP in 8 cases, and ICE in 23 cases. The pre-transplant chemotherapy used in 33 Multiple Myeloma cases was VAD [Vincristine 0.4mg/m^2 i.v. (Continuous infusion) day 1-4, Doxorubicin 9mg/m^2 i.v. (Continuous infusion) day 1-4, Dexamethasone 40mg/day i.v. day 1-4, days 9-12, and days 17-20] in 9 patients. CTDa [cyclophosphamide 500mg/day p.o. day 1, 8, 15, 22, thalidomide 50 mg/day p.o. for 4 weeks increasing by 50mg/day every 4 weeks to 200mg/day, dexamethasone 20mg/day p.o. day1-4 and days 15-18 (Four-week cycle)] in 22 patients, and VTD (Bortezomib 1.3mg/m^2 IV on days 1, 4, 8, and 11 plus thalidomide 200mg/day PO plus dexamethasone 40mg/day PO on days 1-4 and days 8-11) in 2 patients. The pre-transplant chemotherapy used in 5 AML cases FLAG [Fludarabine, Ara-C, G-CSF - (Growth factor)] in 2 cases and FLAG-IDA [G-CSF 5 micro g/kg from day +6 until neutrophil recovery (Growth factor) given by injection under the skin in the tummy or leg from day 1 until counts recover, Fludarabine 30mg/m^2 given via an infusion (drip) over 30 minutes, once a day for 5 days (Days 2-6), Ara-C (Cytarabine) 2mg/m^2 given via an infusion (drip) over 4 hours, once a day (4 hours after the Fludarabine) for 5 days (Days 2-6), Idarubicin 10mg/m^2 given via Bolus injection once a day for 3 days (Days 4-6)] in 3 cases. The pre-transplant chemotherapy was given up to the maximum response as assessed clinically.

Pre-transplant work-up and transplant protocol

Initial evaluation included history, physical examination. Details of prior treatment were recorded. Investigations including complete blood count including differential count; renal and liver function tests; BM examination, MUGA Scan, pulmonary function test, 24 hours urine creatinine clearance and dental check-up were performed for all patients. All patients were informed of the details of the procedure and any potential complications. Written informed consent was obtained. A central line (Perm-a-cath) was inserted.

Stem cell mobilization and collection

The source of Stem Cell in all the transplant cases was peripheral blood. For mobilization of PBSCs, patients received growth factors as an injection of G-CSF 10mcg/kg once daily subcutaneous for 5 days in the nadir of the blood counts (the lowest blood count after chemotherapy) from salvage chemotherapy, or stem cell was collected after cyclophosphamide 1.5mg/m^2 single dose intravenous followed by G-CSF 10µg/kg OD SC, or stem cell was collected following administration of G-CSF alone 10µg/kg once daily subcutaneous.

Table 5. Shows stem cell mobilization in all patients

	NHL 45 patients (37.8%)	HL 36 patients (30.2%)	MM 33 patients (27.7%)	AML 5 patients (4.2%)
Post chemotherapy & G-CSF	6 cases (13.3%)	3 cases (10%)		
Cytoxan & G-CSF	21 cases (46.7%)	22 cases (73.3%)	27 cases (81.8%)	1 case
G-CSF alone	18 cases (40%)	11cases (36.7%)	6 cases (18.2%)	4 cases

Leukapheresis was started on day 5 of G-CSF either when given alone or post-chemotherapy, when CD34+ count in peripheral blood was ≥ 20/μL, from subclavian vein using perm-a-catheter, on COBE-SPECTRA machine the automated or the manual one. Medians of two leukaphereses sessions were performed (Range 1-3). Target CD 34+ count was 5×10^6/kg. A sample of stem cells was obtained and total cell counts were determined using an automated cell counter; the differential cell count was done manually. For CD34 counts, cells were labeled with fluorescein-conjugated anti-CD34 and analyzed using Coulter FC500 flow cytometer to yield an absolute CD34 count. Stem cells were cryopreserved at -80^0C using a 10% DMSO (Dimethyl sulfoxide) in autologous plasma. The procedure was well tolerated, with only 20% of patients having circumoral and peripheral numbness, which solved with calcium gluconate administration.

Conditioning Regimens and supportive care

In Non-Hodgkin 's and Hodgkin' Lymphomas BEAM carmustine (BiCNU), etoposide, cytarabine arabinoside, melphalan] was used in 59 patients (72.8%), BEAC (Melphalan was not available so cyclophosphamide was used) in 15 patients (18.5%), CEAM (BiCNU was not available so it was replaced by CCNU) in 6 patients (7.4%), and Zevalin-BEAM was used in one NHL-DLBCL patient. All Multiple Myeloma patients received melphalan 200mg/m^2 except one patient received melphalan 140mg/m^2 because of renal impairment (24 hour creatinine clearance was < 30mL/min). Acute Myeloid Leukemia patients received cyclophosphamide and Etoposide. The conditioning regimen was tolerated well, 56 patients (46.7%) didn't have significant symptoms, 30 patients (25%) had grade I nausea &vomiting, had 44 patients (28.3%) had grade II nausea, vomiting, and mucositis.

Stem cell infusion

Stem cells were removed from the deep freezer and thawed at room temperature on a water bath. Stem cells were infused 24 h after conditioning regimen. Stem cell viability after thawing ranged from 72% to 85%, cell loss due to cryopreservation ranged from 15%-28%. Autologous blood stem cells were re-infused on day 0 through a central venous catheter. The cells infused were: TNC $10.47 \pm 7.31 \times 10^8$/kg, MNC $4.87 \pm 6.30 \times 10^8$/kg, CD34 + $3.92 \pm 3.64 \times 10^6$/kg, CFU $1328.77 \pm 1094 \times 10^4$/kg. Patients received prophylactic acyclovir 5mg/kg every 8 hours and fluconazole 200mg i.v. once daily starting from Day +1 post stem cell infusion. Ciprofloxacin prophylaxis was started when absolute neutrophil count was ≤ 500/μL. Day 5 onwards patients received growth factor G-CSF 5mcg/kg daily subcutaneous until engraftment. All the blood products transfused during the post- transplant period were irradiated with 25 Gy. Post-transplantation, weekly surveillance for CMV in blood by PCR and twice weekly blood, stool, throat and urine culture were carried out in all patients. Neutropenia was defined as an ANC $<0.5 \times 10^3$/μL. For fever ≥ 37.8°C all patients were subjected to microbial blood cultures, cultures from other sites were collected as clinically indicated, and blood sample for procalcitonin level assessment was withdrawn. For neutropenic fever ≥ 37.8°C all patients initially received broad-spectrum intravenous antibiotics (Piperacillin/Tazobactam and Amikacin), as per the antibiotic guidelines of the center. Later these antibiotics were individually modified according to microbial culture and sensitivity data as well as patient's response. Patient data were obtained from the Stem Cell Transplant Unit, which contains prospectively collected data on all patients undergoing transplant therapy at our center. The post-transplant time period was reviewed for positive culture results starting from the stem cell infusion until day+30 following stem cell transplantation. Blood, stool, throat and urine culture results as well as all pathological data were obtained from the hospital laboratory records and/or medical charts. Culture isolates were recorded as separate infection episodes if isolated >1 week apart for blood or >4 weeks apart for stool. Culture-negative febrile episodes were included in this analysis. The number of infectious episodes was calculated in the whole cohort.

Statistical analysis

Using these data, we performed all statistical analyses using an IBM - compatible computer and the Statistical Package of Social Sciences (SPSS) 17 program for Windows 7 (SPSS, Inc., Chicago, IL.). We calculated the descriptive statistics, including the mean, median, range, number, percentage (Frequency distributions), ratio, for each group of interest and regression analysis of the relevant risk factors.

Table 6. Patients with specific infections

Type of infection	Total patients	Gram + isolates	Total patients	Gram - isolates	Total patients	Mixed Gram + isolates & Gram -isolates	Total patients	Fungi	Total patients
Blood stream infection (Central-venous catheter associated)	17	6		9		1		1	
		Coagulase negative staphylococci	3	E.coli	4	Morganellamorganii, E.coli, klebsiella, Staphylococcus aureus	1	Candida albicans	1
		Staphylococcus aureus	1	klebsiella	2				
		Viridans streptococci	1	acinetobacter	2				
		Staphylococcus epidermidis	1	Chromobacteriumviolaceum	1				
Respiratory tract infections	4			4					
				Klebsiella	1				
				Acinetobacter	1				
				Pseudomonas aeruginosa	1				
				Haemophillus influenza	1				
Gastrointestinal	1			1					
				Salmonella	1				
Urinary tract infection	2			2					
				Multiresistent Pseudomonas aeruginosa	1				
				Enterobacter cloacae-ESBL	1				
Skin & soft tissue	1			1					
				Pseudomonas aeruginosa	1				

Note: Stool analysis showed stongloidiasis in three patients

Results

The mean time for engraftment was 12 days (Range 9-14) in Non-Hodgkin's Lymphomas, 11 days (Range 9-15 days) in Hodgkin' Lymphomas, 12 days (Range 9-14 days) in Multiple Myeloma, 12 days (Range 11-13 days) in Acute Myeloid Leukemia. The mean time for engraftment for all patients was 11 days. The mean duration of severe neutropenia was 7 days (Range 5-9) in all the patients. After transplant the patients received a mean of 2 units packed red blood cells and 4 units of platelets concentrates (Each 1 represents 6 units of pooled random donor platelets). The mean time for platelet transfusion independence was 11 days. The mean duration of growth factor use (Started on day 5 post-transplant) was 9

days. All routine cultures and swabs showed commensal flora. A total of 92 patients (76.7%) had febrile episodes at a median of 7 days (Range -2 to 23 days), whereas 28 patients (23.3%) didn't have any fever spikes. Infections could be documented clinically only in 67 patients (72.8%) where they had culture-negative infections. Infections could be documented clinically and microbiologically, with isolation of in a total of 25 patients (27.2%). The most common sites of infections were blood stream infections in 17 patients (68%), gastrointestinal in one patient (4%), pulmonary infection in 4 patients (16%), skin and subcutaneous tissue in one patient (4%), urinary tract infection (UTI) in two patient (8%). Gram-negative isolates were found in 17 patients (68% of culture-positive febrile episodes). The isolates included Escherichia coli, enterobacter, acinetobacter, klebsiella and Pseudomonas aeruginosa. Gram positive isolates were found in 6 patients (24% of culture-positive febrile episodes). Gram- positive isolates included Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hemolyticus, and Streptococcus viridians. Mixed Gram negative and Gram positive isolates were found in one patient (4%). Fungi were isolated in one patient (4%). Seventeen patients (68%) had Blood stream infections, isolates were Gram-positive in six patients (35.3%), Gram-negative in nine patients (41.2%), mixed Gram-negative and Gram-positive in one patient and fungi in one patient. One patient had enterocolitis due to Salmonella infection and three patients had enterocolitis due to Strongloidiasis. Two patients had Gram-negative urinary tract infections. Table 6 shows the microbiological isolates.

Despite the use of ciprofloxacin for anti-bacterial prophylaxis, seventeen patients (68%) developed infections with Gram-negative organisms; seven of these isolates (41.2%) were sensitive to ciprofloxacin. There was no statistically significant correlation between the number of CD34+ cells infused and hematopoietic recovery in Lymphoma, Myeloma, and AML patients among both sex and in different patients' ages, all patients had prompt comparable myeloid engraftment. Multivariate analyses did not reveal any significant correlation between infection incidence and studied variables cell dose infused (CD34+ count and mononuclear cell count), time to engraftment, the duration of severe neutropenia, the underlying hematological diagnosis and the response to salvage chemotherapy complete remission versus partial remission (Table 7). During the 30-day follow-up period only one patient died secondary to sepsis and respiratory failure.

Table 7. Regression analysis showing febrile episodes didn't correlate with the number of CD34+ cells infused, the time until engraftment, the duration of severe neutropenia, and the underlying hematological diagnosis

Coefficients[a]							
Model	Unstandardized coefficients		Standardized coefficients	t	Sig.	95% Confidence interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
CD34+ × 10^6/kg	.008	.012	.069	.664	.508	-.016	.033
MNC × 10^8/kg	-.005	.007	-.070	-.670	.504	-.019	.009
Time to entgraftment	-.019	.021	-.129	-.949	.345	-.060	.021
Duration of severe Neutropenia	.012	.020	.083	.604	.547	-.028	.053
NHL, HL, MM[b]	.013	.035	.037	.378	.707	-.056	.082

Note: Dependent Variable: INFECTION

Abbreviations: NHL = Non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma;MM = Multiple myeloma

Discussion

In this report we describe the incidence of culture negative and culture-proven microbiological infections during the first 30 days following autologous PBSC transplantation. The autologous transplant recipient is vulnerable to infection during the pre and immediate post engraftment periods. We anticipated a risk of infectious complications. However, twenty eight patients (23.3%) didn't have any fever spikes. A total of 92 patients (76.7%) had short-lived febrile episodes without substantial morbidity and mortality. The observed high incidence of clinically diagnosed infections without cultures and

relatively low incidence of proven infection might be attributable to the prophylactic antimicrobials administered in the post-transplant period. In addition, the use of G-CSF hastening hematopoietic recovery post-transplant may have contributed to the observed incidence of infections were 23.3% of the patients did not have any infections, the shortened post transplant infections with its complications. The G-CSF administered following transplant can reduce the time to engraftment and the risk of post-transplant infections [17]. Also, in a variety of transplant-and non-transplant-related settings G-CSF can enhance neutrophil function [18, 19]. Previous reports describe up to 12% of transplant patients developing invasive infections with Candida species after SCT, with substantial morbidity and mortality [20]. One of the major risk factors for the development of candidiasis is the duration of neutropenia. Fluconazole has demonstrated efficacy in reducing the incidence of both colonization and infection with Candida species in SCT and leukemia patients [21, 22]. C. krusei and C. glabrataare most often resistant to the azole antifungals [21]. Patients with GI colonization with these organisms may suffer added risks for developing bacteremia with enteric bacteria, possibly as a result of tissue damage augmented by the mucosal yeast adherence [22]. We observed a relatively high incidence of blood stream infections (Central venous catheter-associated bacteremia) secondary to Gram-negative isolates as well as a modest number of coagulase-negative Staphylococcus isolates. However, Salazar et al. [23] found that Gram-positive bacteria were responsible for 75% of bacteremias, one-third of which were caused by Staphylococcus epidermidis in a retrospective review of 126 patients undergoing auto-transplantation receiving prophylaxis with ciprofloxacin, itraconazole and acyclovir. A similar incidence of neutropenia- associated complications with a 39% incidence of bacteremia among 66 patients. Gram-positive cocci were the predominant pathogens were found by Kolbe et al. [24]. In a study by Offidani et al. [25] the incidence of infective complications in 150 patients undergoing stem cell transplant was found 13% Gram-positive and 10% incidence of Gram-negative bacteremia, despite prophylaxis with quinolones and fluconazole. A somewhat similar incidence of bacteremia (13%) in 127 breast cancer patients undergoing transplantation, with minimal antibiotic prophylaxis using trimethoprim-sulfamethoxazole in only 6% of patients was reported by Barton et al. [26]. In our review Gram-negative isolates were the predominant pathogens, 42.2% of them were sensitive to ciprofluxacin. In the preengraftment period, the major risk for acquiring infection is neutropenia and altered barrier defenses resulting from the BMT conditioning regimen [2-5]. Another factor is the need for vascular access in this group of patients [2, 3, 21]. The sources of pathogens for infection during this period are the patient's skin flora, oral flora, and GI tract flora [3]. The disruption of the normal barrier defenses allows microorganisms that normally colonize these areas to invade, rendering them pathogenic. The GI flora that usually colonizes the GI tract (i.e., gram-negative organisms, anaerobes, and Candida species) becomes pathogenic in the immunocompromised state [5]. The major concern with the use of prophylactic antibiotics is the development of resistant organisms. Reports of fluoroquinolone resistance in coagulase-negative staphylococci and in E coli have emerged [55, 57]. This might explain the observed relatively higher incidence of Gram-negative isolates in our review. We had modest duration of neutropenia. Besides none of our CMV sero-positive patients had CMV antigenemia and disease during the study period. This is consistent with earlier reports which showed low incidence of CMV antigenemia and disease [27-29].

In conclusion, this retrospective review showed the incidence and consequences of infections following high dose chemotherapy and autologous stem cell transplant in Kuwait Cancer control - Stem Cell transplantation Unit. The duration of severe neutropenia was modest. Infections following stem cell transplant were not life threatening but required specific measures to be reversed. Careful prophylaxis, surveillance and attentive supportive care can limit the infectious hazards.

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