Cardiovascular Status of Patients after Chemotherapy for Haematological Cancers in Jos Nigeria

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Abstract

Heart disease can result from cancers and their treatment, heart failure being the case over time. This is however not our local experience as hardly we find heart failure patients with a past history of cancer or chemotherapy. We therefore decided to evaluate a cohort of patients on follow-up for haematological cancer therapy for cardiovascular status with a view to defining their heart disease burden. Thirteen patients (6 F) with age range of 18 to 55 years on follow-up for haematological cancers underwent cardiovascular examination and relevant data extracted from their files. None of them was in heart failure after a range of 1 to 3 years of therapy. Most however received Prednisolone as adjunctive treatment for their cancers namely: CLL, CML, ALL, AML and Hodgkin's Lymphoma. The low rate of heart disease in our cohort of haematological cancers was surprising. Whether it is due to genetics, environmental factor or adjunctive treatment would require further studies to elucidate. Steroids being anti-inflammatory and anti-fibrotic may be countering inflammatory and fibrotic cardiac damage that chemotherapeutic agents cause.

Keywords: Heart disease; Cancers; Drugs; Nigeria

Introduction

The risk of malignancy is known to rise as the population ages [1]. Though not common place, some of the cancers can involve the heart [2]; as in hepato-cellular carcinoma [3]. Cancers can directly damage the heart before any treatment [4]; but it is the therapy (chemo and radio) that is more deleterious to cardiac function [5]. As more people survive cancer treatment, a pool of people with cardiovascular morbidity is developed; that will strain the health care system. This has given rise to a new field of integrative medicine (Cardio-Oncology/ Onco-Cardiology) between cardiologists and oncologists to manage such cases [6].

Cardiac toxicity follows use of many chemotherapeutic agents, the anthracycline group being the chief culprit; though others like cyclophospahmide and fluorouracil are implicated [7]. It has been a recognized entity for about 50 years following reports of heart failure in children treated with doxorubicin [8]. Cardiotoxic effects of chemotherapy range from mild transient blood pressure elevation and electrocardiographic perturbations to significant arrhythmias, myocarditis, pericarditis, myocardial infarction and cardiomyopathy [7].

In our experience, not many patients presenting with heart failure (HF) give a past history of cancer treatment. With the established fact that systemic cancer treatment exerts a detrimental effect on the cardiovascular system [9], our local experience became a matter of curiosity. We, therefore, decided to clinically assess the cardiovascular status of oncology patients who are on follow-up in the Haematology out-patient clinic of our hospital. This was to ascertain their cardiovascular disease burden; and if possible why heart failure following cancer treatment is a rarity in our experience.

Methods

Between October and December 2011, all subjects on follow-up in the Haematology Clinic of Jos University Teaching Hospital after chemotherapy for haematological cancers were assessed clinically; and relevant information extracted from their records. This was with their full consent and included: age, gender, age at first dose, number of doses till date, date of last dose, cumulative dose, drug(s) used, route of administration, medical history before therapy, current medical therapy, diagnosis of malignancy, any other treatment modality and history of shortness of breath. Physical examination recorded pulse, blood pressure, apex beat, heart sounds, postero-basal crepitations, ascites and hepatomegaly. Any chest X-ray, electrocardiogram and packed cell volume reports found were documented.

Results

Only 13 patients were on follow-up for cancer therapy on the Haematology service at the time; 6 of whom were females. Their ages ranged from 18 to 55 years. Most (11/18) were in their first year of treatment.

The remaining 2 were 2 years and 3 years into treatment. Number of doses ranged from 1 to 8 and last dose from the point of encounter varied from 1 to 88 weeks. Drugs used included Alkylating agents – Cyclophosphamide, Chlorambucil and Decarbazine; Vinca Alkaloids – Vincristine and Vinblastine; Anti-metabolites – Cytosine Arabinoside, Hydroxyurea, Methotrexate; Anthracycline – Adriamycin; Antibiotic – Bleomycin.

Route of administration was mostly parenteral (intra-venous) See Table 1. Prior to chemotherapy, 2 patients had hypertension only, 1 in addition to hypertension had diabetes mellitus and prostatism.

After initiation of chemotherapy new medical symptoms were recorded in 3; one with swelling of the eye lids, one with arthritis and one with Steven-Johnson syndrome.

S/No	Sex	Age	AgeD1	ND	DPC	DCD	Route
1	F	55	54	4	16	C 8g, V 32g, Cy 8 g	IV
2	M	52	52	3	0	C 3g, V 6g, A 100 mg	IV
3	F	45	45	3	6	Ch 392 g	Oral
4	F	45	45	1	1	H 2100 g	Oral
5	F	24	21	4	0	C 3g, V 32 g, Cy 1400 g, M 1600 g	IV/Oral (M)
6	M	43	43	1	0	C 4g, V 6 g, Cy 1g	IV
7	M	21	21	7	0	A 3.5 g, B 140U, Vb 84 mg D 5.1 g	IV
8	F	30	30	3	0	C 4 g, V 14 mg, Cy 1.4 g	IV
9	F	51	51	3	2	Ch 300 mg	Oral
10	M	29	29	2	0	H 2100 g	Oral
11	M	55	55	8	12	V 16 mg, C 8 g, A 200 mg	IV
12	M	55	53	8	88	C 8 g, V 16 g	IV
13	M	18	18	8	12	C 2.5 g, V 12 g	IV

Key – Age (in years), Age D1: age at first dose, ND: number of doses, DPC: duration post chemotherapy (in weeks), DCD: doses of drug combination, C: Cyclophosphamide, V: Vincristine, Cy: Cytosine Arabinoside, A: Adriamycin, Ch: Chlorambucil, H: Hydroxyurea, M: Methotrexate, B: Bleomycin, Vb: Vinblastine, D: Decarbazine

Table 1: Demographic characteristics of study patients

As at the time of evaluation, shortness of breath was recorded in only one of them. But for 2 persons with a bradycardia of 56/minute, pulse rate was normal in all of them ranging from 60 to 100/minute. Blood pressure elevation>140/90 mm Hg was recorded in 5 of them, 2 of whom had given a prior history of hypertension. Abdominal examination was normal except in 3 people, 2 with organomegaly and 1 with only ascites. Chest X-ray records were normal in 10/11 who had records. Only 1 of the X-rays showed cardiomegaly. Electrocardiogram was normal in all but three with left ventricular hypertrophy, sinus bradycardia and left anterior hemi block.

As stated, they all had haematological cancers – 5 (non-Hodgkin's Lymphoma), 2 (chronic lymphocytic leukaemia) 2 (chronic myeloid leukemia), 2 (acute lymphoblastic leukemia) 1 (Hodgkin's lymphoma) 1 (acute myeloid leukemia). Adjunctive treatment consisted of Prednisolone (9), and Zyloric (9); both drugs being combined in 6. Packed cell volume (PCV) ranged from 21% to 43% with 9 patients having values less than 35%. See Table 2.

S/No	Diag	MH	P	BP	PCV	OT	ECG	Remarks
1	NHL	BP	76	136/80	NA	Pred/Zy	LVH	D/A
2	NHL	Nil	56	146/84	43%	Pred/Zy	SB	D/A
3	CLL	BP	100	200/110	34%	Pred	N	D/A
4	CML	Nil	80	112/60	33%	Zy	LAHB	NCXR
5	ALL	HBV	68	106/76	38%	Pred/Zy	N	Nil
6	AML	Nil	60	136/86	25%	Pred	N	Nil
7	HL	Nil	56	120/80	30%	Nil	N	Nil
8	ALL	Nil	100	130/90	30%	Pred	N	Nil
9	CLL	Nil	100	144/90	29%	Zy	N	Swollen eye
10	CML	Nil	96	124/70	21%	Zy	N	Nil
11	NHL	Nil	60	134/84	30%	Pred/Zy	N	Nil
12	NHL	BP/DM	72	140/96	43%	Pred/Zy	N	LUTS
13	NHL	Nil	72	120/80	32%	Pred/Zy	N	S/ Johnson

Key: Diag – Diagnosis, MH – Medichal history, P – pulse, PCV – Packed cell volume, BP – Blood pressure, OT – Other treatment, ECG – Electrocardiogram, NHL – Non-Hodgkins lymphoma, NA – Not available, Pred – Prednisolone, Zy – Zyloric, LVH – Left ventricular hypertrophy, D/A – Displaced apex, CLL, -Chronic lymphocytic leukaemia, CML – chronic myeloid leukaemia, LAHB – Left anterior hemi block, NCXR - Normal Chest X ray, ALL – Acute lymphocytic pneumonia, HBV – Hepatitis B virus, N – Normal, AML, Acute myelocytic leukaemia, HL – Hodgkin's lymphoma, DM – Diabetes mellitus, LUTS – Lower Urinary Tract Symptoms, S/Johnson – Steven Johnson syndrome

Table 2: Clinical characteristics of study patients

Discussion

Many chemotherapeutic agents used in cancer therapy affect the heart adversely. Apart from haematological cancers, those used to treat breast, ovarian and gastrointestinal and renal cancers can also lead to cardiac dysfunction. Examples include monoclonal antibodies used to treat breast cancers and Interleukins used to treat renal and skin cancers [9]. These drugs are more likely to precipitate heart failure if used in combination with other cardio toxic chemotherapy [10]. For instance used alone, Trastuzumab has been reported to be associated with up to 2% risk of overt cardiac disease, rising up to 16% when used in combination with anthracyclines and alkylating agents [10]. This restricts its applicability in clinical practice, prompting recommendation of careful patient selection. We settled for patients treated for haematological cancers because there was a ready cohort on follow up in our facility. Expectedly age, current life style and premorbid diseases can impact on cardiovascular presentation of patients the post chemotherapy. Our cohort was relatively young (18 to 55 years) with only 3 out of 13 having background cardiovascular disease. None of them currently smoked or abused alcohol. This limited observation (in number, type of cancer and post-chemotherapy duration) did not reveal any patient with history or physical findings suggestive of heart disease. The only case with shortness of breath on strenuous activity had the lowest PCV which could explain the symptom. This is the curiosity and may be why in our clinical experience, heart failure patients hardly give a history of chemotherapy.

In the immediate post-chemotherapy period, evidence of cardio toxicity includes arrhythmias, ischemia, vasospasm, thromboembolism and myo-pericarditis [11]. Chronic intake results in left ventricular dysfunction with or without overt heart failure and arterial hypertension among others [12]. The chemotherapeutic agents are known to have unique cardio toxic effects [9]. Anthracyclines which were used often here result in left ventricular dysfunction in a dose-dependent manner; due to direct myocardial injury of formed free radicals [13] and inhibition of genetic materials [14]. They (Anthracyclines) are cytotoxic antibiotics – Daunorubicin and Doxorubicin; of fungal origin demonstrating clear cause and effect dose relation on the heart [15]. When dose is reduced to spare the heart, remission rate and survival are adversely affected. Significant cardiac morbidity was not the experience here; as with use of alkylating agents. Despite the use of multiple drugs in the regimen, features suggestive of heart failure were lacking; not even with low PCV except in the patient with the lowest value. Other co-morbidities that make for increased risk like youth, female gender, pre-existing hypertension [16] made no impact here; neither did intravenous bolus administration or use of combined therapeutic agents [17]. The dearth of symptomatology of HF here may be due to reliance on physical examination only. This alone is said to miss over 50% of cases in early and reversible chemotherapy induced HF [18]. It may also have to do with shorter duration post-therapy of our cohort. Most of our patients were under 3 month's post cumulative exposure when seen; only one being close to 2 years. We are not in a position to tell whether others who may have received chemotherapy for haematological cancers but did not show up for follow-up were dead or defaulted for various socio-economic reasons. Though cardio toxic effects could appear acutely, within 1 week, the more clinically recognized variety is the chronic progressive condition which may present within a year [19] or progress more slowly [20]. Interestingly incidence is said to be more 4 to 10 years after therapy, especially with anthracyclines [21]; which was not the case here.

Incidence of symptomatic heart failure during or within the 1st year is low and stands at about 3% [22]. Preventing cardio toxicity helps to maximize the benefit of these chemotherapeutic agents one sure step to attain of which is adjunctive cardio protective drugs. Drugs like beta-blockers (Carvedilol) or angiotensin receptor blockers (Valsartan) when used as adjunctive treatment are known to block acute toxic effects of Anthracyclines that lead to early and late cardio toxicity [23]. Our patients did not receive any such drugs on the side, what was prominent as adjunct was Prednisolone. Doxorubicin induced cardiomyopathy is said to result from inflammation and fibrosis due to Endothelia 1 mediated cardiac injury [24]. This damage being inflamer stands to be blocked by anti-inflammatory and fibrotic effects of steroids, exemplified here by Prednisolone. This explanation is speculative and should be further explored to see if steroids block cardio toxic effects of anti-cancer drugs. This is pertinent when viewed in the background of a study by Foss et al. [25] where steroid pre-medication blunted hypersensitivity reaction that followed infusion of drugs used in some haematological malignancies or renal and skin malignancies treated with Interleukins [9].

In conclusion, cytotoxic treatment for haematological cancers did not seem to provoke or precipitate HF in our center. Whether this is due to genetics, adjunctive use of Prednisolone in many or short duration will require a well-designed study including a larger population to determine.

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