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Original Article

Clinical use of Carica papaya leaf extract in chemotherapy induced thrombocytopaenia

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Abstract: Managing chemotherapy induced thrombocytopaenia is still a challenge. A few animal studies showed positive effects of *Carica papaya* (CP) on thrombocytopaenia. This study examined effect of CP leaf extracts on chemotherapy induced thrombocytopaenia. Thirty subjects were recruited as 'case' and thirty as 'control'. 'Cases' were cancer patients with chemotherapy induced thrombocytopaenia. CP capsule (290 mg) was given twice daily in 'cases' for 5 consecutive days or till to normal platelet count. Platelet count was observed at 5 days intervals or more frequently. Then pre and post-treatment platelet counts were compared individually in both arms by statistical tests. Response was evaluated in twenty eight (28) 'cases'. As a whole, platelet count increased from 101.93 ± 26.15×10^3/uL to 173.75 ± 29.98×10^3/uL (P=1.37225E-09) in 'cases' and 99.36 ± 16.62×10^3/uL to 101.75 ± 16.03×10^3/uL (P=0.11) in 'controls'. Treatment related adverse events were not found. Thus CP leaf extracts significantly increased thrombocytes in post-chemotherapy cancer patients.

Keywords: Carica papaya leaf, chemotherapy, thrombocytopaenia

Introduction

Cancer prevalence in the world is around 32.5 million [1]. With the rising trend of cancer cases, the use of myelo-suppressive drugs is increasing. Availability of several novel haematopoietic growth factors has significantly reduced neutropaenia and anaemia but no established and effective single agent is available in current oncology practice to combat thrombocytopaenia [2]. Chemotherapy induced thrombocytopaenia have become more prevalent. Presently, management of chemotherapy induced thrombocytopaenia remains with dose reduction, treatment delay, schedule alteration and platelet transfusion. Therefore, thrombocytopaenia can affect treatment efficacy, quality of life and healthcare costs, and often associated with increased morbidity and occasional mortality [3-5].

Despite extensive research in the past decade, the only FDA-approved drug for the management of chemotherapy induced thrombocytopaenia has been recombinant interleukin-11 (rhIL-11) [6]. It stimulates maturation and proliferation of megakaryocyte so as to maintain platelet production [7]. However, its limitations are modest effect and narrow therapeutic index [8, 9]. It also neutralizes antibodies to pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) which made a negative impact on further clinical development of this product [8]. Therefore, search for cost effective anti-thrombocytopaenic agent is a time demanding concern.

Carica papaya (CP), belongs to the plant family Caricaceae, is an economically important fruit crop worldwide [10]. Many scientific works have been carried out to evaluate the benefit of different parts of papaya plant including fruits, seeds, leaves, rind, shoots, roots or latex [11]. The leaf is considered non-toxic as its lethal dose is >15 g/kg body weight [12]. It contains

Table 1. 'Cases' and 'controls' characteristics

		'Cases' (%)	'Controls' (%)
Age (years)	Mean	53.04	52.75
	Range	28-80	30-78
Gender	Male	19 (67.85%)	18 (64.29%)
	Female	09 (32.15%)	10 (35.71%)
Socioeconomic condition	Lower Class	03 (10.71%)	04 (14.29%)
	Middle Class	23 (82.14%)	18 (64.29%)
	Upper Class	02 (07.14%)	06 (21.43%)
Educational level	Illiterate	03 (10.71%)	02 (07.14%)
	Secondary	10 (35.71%)	12 (42.86%)
	Higher Secondary	07 (25%)	08 (28.57%)
	Graduate	08 (28.57%)	06 (21.43%)
Cancer	Gastrointestinal (GIT)	10 (35.71%)	12 (42.86%)
	Genitourinary (GU)	06 (21.43%)	08 (28.57%)
	Head & Neck	06 (21.43%)	06 (21.43%)
	Breast	04 (14.29%)	01 (3.57%)
	Carcinoma Unknown Primary (CUP)	02 (07.14%)	01 (3.57%)
Stage	Early (I & II)	08 (28.57%)	06 (21.43%)
	Advanced (III & IV)	20 (71.43%)	22 (78.57%)
Comorbidities	Hypertension & IHD + 4	12 (63.16%)	13 (46.43%)
	Diabetes + 1	05 (26.32%)	06 (21.43%)
	COPD	01 (5.26%)	02 (07.14%)
	Others	01 (5.26%)	01 (3.57%)

Table 2. History of previous cancer treatment

Chemotherapy	No of patients	Onset of thrombocytopaenia (days)
Oxaliplatin + 5FU + Leucovorin	5	After 9-11 (range)
Oxaliplatin + Capecitabine	4	After 7-11 (range)
Paclitaxel + Carboplatin	3	After 7-8 (range)
Concurrent chemoradiation with Cisplatin	2	After 5-6 (range)
Gemcitabine + Carboplatin	2	After 7
Bevacizumab + Gemcitabine + Carboplatin	1	After 6
Gemcitabine + Carboplatin + Docetaxel	2	After 6
5-FU + Carboplatin	1	After 18
Docetaxel + Carboplatin	1	After 19
Gemcitabine + Oxaliplatin	2	After 7-8 (range)
Gemcitabine	2	After 6
Bleomycin + Etoposide + Cisplatin	1	After 2
Cisplatin + Ifosfamide	1	After 5
Trastuzumab + Vinorelbine	1	After 18

several active ingredients like papain, chymopapain, alkaloids, flavonoids, cystatin, tocopherol, ascorbic acid, cyanogenic-glucosides, glucosinolaid, which have the activity to reduce lipid peroxidation level and raise antioxidant activity [13, 14]. Its active component alkaloids, flavonols, flavonoids, saponins, tannis, cardia glycoside have showed effectiveness against inflammation [15]. Contraceptive efficacy of CP leaves and seeds has been documented earlier [16, 17]. Romasi *et al*. has demonstrated antitumor, antibacterial and immunomodulatory activity of CP leaves extract [18]. Preclinical studies in mice demonstrated encouraging activity of CP powder in increasing platelet count [11]. Recently in vitro study showed that CP leaves extract exhibited significant inhibition of hemolysis probably due to its membrane stabilizing potency [19]. With the above contemplation, efficacy and safety profile of papaya leaf extracts was investigated on chemotherapy induced thrombocytopaenia.

Materials and methods

Materials

Treatment materials were obtained from fresh matured papaya leaves. At first leaves were washed thoroughly with plain water. Then leaves were blanched at 60-65°C for 5 minutes, soaked into water containing 1% sodium benzoate for 1 to 1.5 minutes at 90-95°C, blended with water 50 vol.% to prepare papaya leaves juice, filtered through fresh cotton bed & whatman No.1 filter paper, freeze dried and grinded into granules. The granules were then passed through a sieve of 15-20 mm. The granules were put into capsules, which contained 290 mg papaya leaf granules. Capsules were then stored in a sterile container and labeled.

Table 3. Overall efficacy of CP leaf extracts in 'cases'

'Cases' number (N)=28	Baseline platelet count (×10³/uL)	Platelet count (×10³/uL) after treatment with CP capsules (within day-1 to day-12)
Mean ± standard deviation	101.93 ± 26.15	173.75 ± 29.98
P value (one tailed, dependent t test)	1.37225E-09 (<0.05) (Statistically significant)	
Minimum baseline	60	170 (on day-5)
Maximum baseline	140	160 (on day-5)

Table 4. Overall efficacy without CP leaf extracts in controls

'Control' number (N)=28	Baseline platelet count (×10³/uL)	Platelet count (×10³/uL) without intervention (within day-1 to day-12)
Mean ± standard deviation	99.36 ± 16.62	101.75 ± 16.03
P value (one tailed, dependent t test)	0.10532466 (>0.05) (Not significant)	
Minimum baseline	64	80 (on day-5)
Maximum baseline	138	140 (on day-5)

Subjects

The study was conducted on 30 (thirty) 'cases' and 30 (thirty) 'controls' in four specialized hospitals of Bangladesh from February, 2014 to May, 2015. Both 'cases' and 'controls' received cytotoxic drugs but only 'cases' were intervened. Informed written consent was taken from all 'cases' and 'controls'. Ethical clearance was obtained from competent authority. 'Cases' were treated with CP leaf extract capsules, twice daily for every 5 days but the 'controls' were not given any. Blood samples of 'cases' and 'controls' were assessed at 5 days intervals for platelet count, haematocrit and blood chemistries such as liver enzymes, electrolytes and creatinine. As optimum dose response period was unknown, randomly even earlier, blood samples were assessed in some cases. Two 'cases' were excluded from data analysis for disappearance.

Statistical analysis

Data were compared and evaluated by one tailed dependent student t-test and statistical correlation, which were done by Microsoft Excel version 10 (Microsoft Corporation Redmond WA, USA). *P* value of less than 0.05 was considered statistically significant with confidence interval of 95%.

Results

Mean age of the 'cases' and 'controls' were 53.04 years and 52.75 years respectively. In 'cases' and 'controls' men and women were 67.85% & 32.15% and 64.29% & 35.71% respectively. Around 92.85% 'cases' and 78.58% 'controls' were from lower and middle socioeconomic condition respectively. Enrolled 'cases' & 'controls' were suffering from head & neck, breast, CUP, GIT, GU cancers. Reported comorbidities were cardiovascular, diabetes and COPD (**Table 1**).

Thrombocytopaenia was observed in 'cases' & 'controls' who received at least one of the cytotoxic agents causing thrombocytopaenia as a single agent or in combination. These were 5-FU, Bleomycin, Etoposide, Ifosfamide, Cyclophosphamide, Paclitaxel, Docetaxel, Carboplatin, Oxaliplatin, Gemcitabine, Capecitabine and Cisplatin with radiation (**Table 2**).

Platelet count in 82.14% 'cases' normalized within 5 days of taking CP leaf capsules. Statistical analysis showed significant difference (1.41363E-07) in platelet count of pre and post CP capsule treated cases. For the patients treated with the CP capsules, platelet count generally increased from thrombocytopaenic level after 5 days (from (107.8 ± 24.17)×10³/uL to (153.6 ± 4.97)×10³/uL, *P* value=0.012). Remarkably, normalization of thrombocyte counts was faster in 5 'cases' within 3 days, even at 1 day but delayed in 5 'cases' for up to 12 days. Rising of mean platelet count in delayed response group was also statistically significant as it increased from (96.2 ± 24.70)×10³/uL to (179.80 ± 82.20)×10³/uL, *P* value=0.003. For the 'control' group, the overall level of platelet count did not significantly increase; (99.36 ± 16.62)×10³/uL to (101.75 ± 16.03)×10³/uL), *P* value=0.11 (**Table 4**).

In present study, 100% 'cases' responded with CP leaf extract capsules. Overall, level of platelet count increased from (101.93 ± 26.15)×10^3/uL to (173.75 ± 29.98)×10^3/uL in 'cases' (**Table 3**). The lowest and highest baseline level of platelet count were (60×10^3/uL & 140×10^3/uL) and (64×10^3/uL & 138×10^3/uL) in 'cases' and 'controls' respectively (**Tables 3**, **4**).

Discussion

The result of the study showed that CP leaf extract capsules normalized level of platelet count within 1-12 days (**Table 3**). In a Chinese study, Sun *et al*. described the action of rh interleukin-11, a recognized thrombopoietic growth factor, which raised platelet count from (30.18 ± 12.13)×10^3/uL to (226.25 ± 163.91)×10^3/uL in 14 days [20]. In 2006, Lei and his co-workers framed the time recovery of rhIL-11 2-18 days [21]. Therefore, it may be argued that CP leaf capsules are more effective than the expensive rhIL-11 in normalizing the level of platelet count in post chemotherapy thrombocytopaenic cancer patients.

In this study, no adverse effect was observed, when used in the treatment of chemotherapy induced thrombocytopaenia. No significant change was found in pre and post-treatment level of haematological and biochemical values. No sign or symptom was found over the treatment period and there was no treatment related death. Thus oral use of CP leaf capsules was found safe for the management of chemotherapy induced thrombocytopaenia.

CP leaf extract capsules demonstrated a clinically & statistically noteworthy outcome in raising platelet count on chemotherapy induced thrombocytopaenia. The present study is calling for randomized clinical trial of CP leaf extract ingredients.

Disclosure of conflict of interest

None.

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