ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 07, pp.34209-34212, July, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

UTILITY OF CARICA PAPAYA EXTRACT IN TREATMENT OF CHEMOTHERAPY INDUCED THROMBOCYTOPENIA IN HUMANS, EXPERIENCE OF A TERTIARY CARE HOSPITAL IN KASHMIR

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ARTICLE INFO

Article History:
Received 15th April, 2016
Received in revised form
20th May, 2016
Accepted 23rd June, 2016
Published online 16th July, 2016

Key words:

CIT-Chemotherapy induced thrombocytopenia,
Swiss count—capsule form of Carica Papaya of pharma division Friska India, SDAP- single donor apheresis plasma, PC- platelet concentrates. CPLE-Carica papaya leaf extract. TPO- thrombopoitin.

ABSTRACT

Chemotherapy is still the standard of care in management of solid tumors. Chemotherapy has a common toxicity of myelosuppression. Some chemotherapy regimens cause either thrombocytopenia or bi-cytopenia. Living in developing countries pose another challenge in treatment of myelosuppression, and to continue timely chemotherapy.

Aim: To study the role of Carica Papaya extract in treatment of chemo induced thrombocytopenia in low socio-economic strata of patients.

Methods: It was a prospective study, in which patients of different solid tumors were enrolled. Haemogram of all patients was recorded when they got myelosuppression on continuation of chemotherapy. Carica Papaya plant extract in the form of capsule (Swiss count from Friska) 700 to 1400 mg a day in two divided doses was given for a period of five days. Repeat haemogram was carried out on sixth day.

Results: There was median nine fold rise in platelet count and median 1.65 fold rise in total leucocyte count in cases, while as in controls; there was 4.3 fold rise in platelet count.

Conclusion: This is a very economical method of treatment of chemotherapy induced myelosuppression and very much recommended for developing countries, to decrease cost of treatment significantly.

Citation: Javvid Muzamil *et al.* 2016. "Utility of Carica papaya extract in treatment of chemotherapy induced thrombocytopenia in humans, experience of a tertiary care hospital in Kashmir", *International Journal of Current Research*, 8, (07), 34209-34212.

INTRODUCTION

Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic toxicity of myelosuppressive and ablative therapy. Severe or persistent CIT not only has a risk of life-threatening spontaneous hemorrhage, but also may necessitate reduction and/or delay in treatment doses. (Bhatia *et al*., 2007) Allogeneic platelet transfusions remain the mainstay of treatment for severe or symptomatic CIT. Although the presence of a thrombopoietic-specific cytokine was first suggested in 1958, TPO was not cloned until 1994. (Kaushansky *et al*., 1995; Lok *et al*., 1994) Given the success of granulocyte colony stimulating factor and erythropoietin therapy in promoting lineage-specific hematopoiesis, TPO agents were anticipated to have great therapeutic potential in CIT and other thrombocytopenic disorders. Focus then shifted to nonimmunogenic, second generation thrombopoietin receptor (c-Mpl) peptide agonists that shared no sequence homology with native TPO. (Kuter, 2007) Two of the c-Mpl agonists, AMG531 (Bussel *et al*., 2006) and eltrombopag, (Bussel *et al*., 2006) then were developed for same cause. AMG531 is also being tested in myelodysplastic syndrome and cytopenias associated with non-Hodgkin's lymphoma and a number of other cancer. Eltrombopag is also being tested in hepatitis-C-associated thrombocytopenias and other trials in sarcoma, metastatic disease, renal impairment, and hepatic impairment are being initiated. (Jenkins *et al*., 2007; Erna C. Arollado *et al*., 2013) Eltrombopag is an orally available small molecule (molecular weight 547 D). In a randomized, double-blind, placebo-controlled trial, platelet counts increased to more than 50 $x10^9$/L in 70% and 81% of patients treated with 50 mg and 75 mg daily doses, respectively. (Jenkins *et al*., 2007) No significant adverse events were seen. Herbal plant extracts of C. Papaya has been proved for augmentation of platelet count in multiple studies in animals, rodents and humans. In a study conducted in Philippines in 2013 for same, there was 125% increase in platelet count form basal level. (Erna C. Arollado *et al*., 2013)

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Original study

Aim of study

To study the role of Carica Papaya extract in treatment of chemo induced thrombocytopenia in low socio-economic strata of patients.

Method of study

It was a prospective study, in which patients of different solid tumors were enrolled, their disease status and basal haemogram, type and number of chemotherapies received were noted down. We divided patients into cases and controls with matching in all characteristics. This study was carried in four months. Haemogram of all patients was again recorded when they got myelosuppression on continuation of chemotherapy. Carica Papaya plant extract in the form of capsule (Swiss count from Friska) 700 mg a day in two divided doses if platelet count was more than 50 × 10^3/ µl and 1400 mg a day in two divided doses if platelet count was less than 50 × 10^3/ µl, for a period of five days. Repeat haemogram was carried out on sixth day. In controls, no intervention was done except in two patients who received PC's.

OBSERVATION AND RESULTS

A prospective study was conducted in a tertiary care hospital in oncology department, with this department in place for last 28 years and cancer registry in place for last 15 years. Since we face poor strata patients and this was the need of the hour to decrease the cost of supportive treatment.

A total of 160 patients were enrolled for this study. Median age was 58 years, with oldest patient of 75 years and youngest of 35 years. Male to female ratio was 3:5. Different types of malignant conditions enrolled are indicated in Table 1, with commonest malignancy enrolled was non-small cell carcinoma lung followed by carcinoma breast. Average number of chemotherapy courses received by patients was four, with minimum of two and maximum of six, when they developed myelosuppression. Commonest regimen incriminated was Gemcitabine and Carboplatin in 120 patients followed by Cisplatin and Paclitaxel in 20 patients. The base line haemogram of these 160 patients is listed in Table 2. The median haemoglobulin was 12.0 gm/dl, median platelet count was 120 × 10^3 /µl and median Total leucocyte count was 6.9 × 10^3 /µl. All these patients were on active chemotherapy and the haemogram was recorded while patients got myelosuppression and it was on average day 15th today 20th of post chemotherapy. These patients were equally divided into cases and controls. All cases received this herbal extract and all controls were observed only except two patients who presented with symptomatic critical thrombocytopenia of 12 × 10^3 /µl, received PC's. The median haemoglobulin was 7.0 gm/dl, median platelet count was 12 × 10^3 /µl and median total leucocyte count was 2.9 × 10^3 /µl in cases, while as median haemoglobulin was 7.5 gm/dl, median platelet count was 15 × 10^3 /µl and median total leucocyte count was 2.6 × 10^3 /µl in controls (Table 3). All cases received Carica Papaya extract (Cap Swiss count) in two different dosages for five days. If patient had platelet count of more than 50 × 10^3 /µl, he received 700 mgs in two divided doses and if platelet count was less than 50 × 10^3 /µl, he received 1400 mgs in two divided doses.

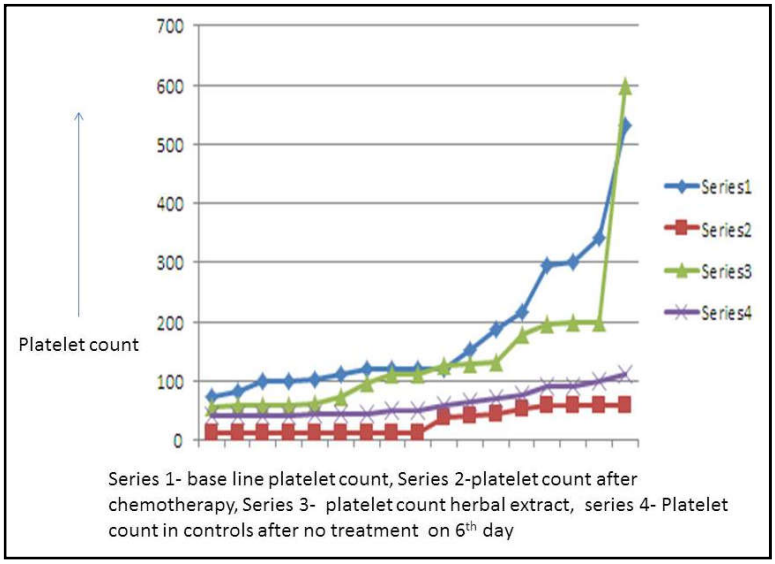

Table 1. Types of tumors and chemotherapy regimens used

Tumor type	Treatment regimen used	Number of patients		Average courses of chemotherapy before CIT in both
		Cases	Controls	
Non-small cell lung	Gem-Carb	35	35	4
Breast	Gem-Carb	10	10	4
GE junction with Stomach	Pac-Cisplatin	10	10	4
Ovary	Gem- Carb	10	10	2
Gall bladder	Gem-Carb	5	5	2
Rectum	CAPOX	5	5	6
Non-Hodgkin's lymphoma	CHOP	5	5	6

Gem-Carb= gemcitabine 1gm /m^2 on day 1 & 8 plus carboplatin AUC 5 every 3 weekly, CAPOX= capcitabine 1000mg/m^2 twice a day for 14 days plus oxaliplatin 130mg/m^2 every 3 weekly, CHOP= Cyclophosphamide 750mg/m^2 ,doxorubicin 50mg/m^2,vincristine 1.4mg/m^2 plus prednisolone 100mg every 3 weekly. Pac—Paclitaxel 175 mg/ m^2& Cisplatin 70 mg/m^2every 3 weekly.

Table 2. Basel haemogram of enrolled patients

Parameter	Minimum value		Median value		Maximum value	
	Cases	Controls	Cases	Controls	Cases	Controls
Haemoglobulin(gm/dl)	8.2	8.0	12.0	12.2	14.0	13.8
Total leucocyte count($\times 10^3$ /µl)	2.1	2.5	6.9	6.5	10.4	11.0
Platelet count($\times 10^3$ /µl)	72	78	120	110	532	445

Table 3. Chemo induced myelosuppression haemogram

Parameter	Minimum value		Median value		Maximum value	
	Cases	Controls	Cases	Controls	Cases	Controls
Haemoglobulin(gm/dl)	6.5	6.3	7.8	7.5	11	11.5
Total leucocyte count($\times 10^3$ /µl)	0.9	1.0	2.9	2.6	8.4	8.3
Platelet count($\times 10^3$ /µl)	11	12	12	15	60	66

Table 4. Post Swiss count (Day 6th) haemogram

Parameter	Minimum value		Median value		Maximum value	
	Cases	Controls	Cases	Controls	Cases	Controls
Haemoglobulin(gm/dl)	6.5	6.8	8.0	7.5	11.5	11.4
Total leucocyte count($\times 10^3$ /µl)	1.2	1.2	4.8	3.8	7.8	8.9
Platelet count($\times 10^3$ /µl)	56	40	110	65	600	110

In 2(2.5%) of our patients, critical thrombocytopenia of 11 × 10^3 /µl was seen and both presented with epistaxis, in addition to Swiss count, one received SDAP one session and other received four PCs. Repeat haemogram was performed on sixth day morning in all cases and controls. Patients (cases) who received Swiss count, revealed median haemoglobulin of 8.0 gm/dl, median platelet count was 110 × 10^3 /µl and median total leucocyte count was 4.8 × 10^3 /µl (Table 4). In controls, haemogram revealed median haemoglobulin of 7.5 gm/dl, median platelet count was 65 × 10^3 /µl and median Total leucocyte count was 3.8 × 10^3 /µl (Table 4) None of these patients were on GCSF or GM CSF or TPO products. The median rise of platelets with this herbal product was 9.16 fold, median rise of total count was 1.65 fold and there was almost no rise in haemoglobulin, while as in controls, median rise of platelets was 4.3 fold and median rise in total count was 1.46 fold (Figure 1). This drug was very effective when used in patients having platelet count of more than 50 × 10^3 /µl as compared to patient with less than this. It was seen there was more than 2 fold rise in platelet count in cases as compared to controls. As for side effect profile is concerned, 12.5% of patients developed grade 1 vomiting and 12.5% experienced epigastric burning. There was no other side effect reported by patients. There was no pediatric patient or leukemic patient enrolled in study. We conclude, this is the most economical way of treatment of CIT especially in low socio economic regions and there has been no such study in literature except in patients of viral dengue. Further we will assess its role in pediatric patients and in leukemic.

DISCUSSION

Thrombocytopenia is a common problem in patients with cancer. It can result from chemotherapy or radiation treatment, or from the underlying disease itself. Thrombocytopenia creates a number of problems in the care of a cancer patient. At platelet counts < 10,000/µL, spontaneous bleeding is increased. At platelet counts < 50,000/µL, surgical procedures are often complicated by bleeding. At platelet counts < 100,000/µL, chemotherapy and radiation therapy are administered with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding. (Kuter, 2013) Clinicians' responses to thrombocytopenia in a cancer patient vary. Reduction of the dose intensity of chemotherapy or radiation is common; more effective regimens with thrombocytopenic toxicity may be avoided; and treatment may even be precluded. Platelet transfusion is often the only readily available treatment. The platelet has a normal lifespan of 8 to 10 days. After many types of chemotherapy, the platelet count generally starts to drop by day 7 and reaches its nadir at day 14, with a gradual return back to baseline by day 28 to 35. (Shimazaki *et al*., 1997) The incidence, severity, and duration of thrombocytopenia vary with the chemotherapy regimen. Most non-myeloablative chemotherapy regimens were developed to minimize thrombocytopenia and the need for platelet transfusions. Thus, most standard regimens are associated with relatively low rates of dose-limiting thrombocytopenia. The response tosignificantchemotherapy-induced thrombocytopenia has not been codified in guidelines, and there are no studies to guide the appropriate approach to management of patients with this condition. The direct costs of treating thrombocytopenia in the cancer patient can be readily assessed. For example, a platelet transfusion costs about $3,000 per event (calculated as the cost of a single apheresis product or a pool of six random donor concentrates) and a transfused unit of RBCs costs about $1,300–$3,500. A week of antifibrinolytic treatment with epsilon aminocaproic acid (6 g/d) is $280, and with tranexamic acid (6 g/d) is $290. A week of thrombopoietin receptor agonist treatment with romiplostim (2 µg/kg/wk) is about $1,400, and with eltrombopag (75 mg/d) is about $2,000. (Data are from Partners Healthcare Center for Drug Policy.) Oprelvekinat 50 µg/kg daily costs $2,366 (average wholesale price) for a week of treatment. However, no attempt has been made to address the overall costs of thrombocytopenia and its treatment in patients with cancer. The simple issues of chemotherapy delay and dose reduction carry with them costs in material and space

utilization, while the larger issue of reduced dose intensity in some settings translates into the costs of life lost. While guidelines exist to guide the rational administration of platelet transfusions, there are few data and no established guidelines to guide rational reduction in chemotherapy dose or frequency, which is often the first response to treating thrombocytopenia in the setting of cancer.

Studies on herbal medicinal products for platelet augmentation are consistently increasing due to the limited supportive treatments available for thrombocytopenic disorders.

So, because the financial constraints and many studies available in rodents and humans for augmentation of platelet count by CPLE, we got encouraged to do same study in CIT patients. A pilot study was conducted in India on patients of Dengue, in which baseline platelet count was 64.79×10^3 /µl and with five days treatment of CPLE, it raised by 61.6% in test group than control group. (Gowda *et al*., 2015) As for cost of treatment is concerned, it was 500 to 1000 Indian rupees. In our study we got median rise of nine fold from base line count of platelets. There was around 1.65 fold rise in TLC count and no rise in HB in treatment arm while as in controls we got 4.3 fold rise in platelet count.

So, it was seen that there was a double response of platelets in cases compared to controls. Side effect profile was very safe and was consistent with previous studies done in dengue patients.

Conclusion

Swiss count capsules (C. Papaya) is the cheapest modality available for treatment of CIT, which is highly cost effective and safe. In order to prevent delays in three weekly chemotherapy regimens which are based on platinum and gemcitabine chemotherapy drugs, this drug should be used from day 15^{th} today 19^{th} of every course in either adjuvant or palliative setup. If platelet count is very low and symptomatic, one has to use platelet transfusion in addition to CPLE.

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