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Research Article

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The Effect of Bovine Colostrum on the Absolute Neutrophil Counts of Pediatric Patients with Acute Lymphocytic Leukemia Undergoing Chemotherapy: A Double Blind Randomized Placebo Controlled Study

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Abstract

Background: *Changes in the blood counts mainly leukopenia and neutropenia in patients with Acute Lymphoblastic Leukemia (ALL) are common adverse events following chemotherapy. These commonly delays further administration of chemotherapeutic agents thereby potentially affecting therapeutic outcomes. Bovine colostrum has shown some promises in different fields of medicine and one claim is its use in prevention of neutropenia. However, there are no studies to support such claim*

Objective: *The general objective of this study is to determine the efficacy of bovine colostrum in preventing neutropenia among patients with ALL receiving chemotherapy.*

Methodology: *This is a randomized, double blind, placebo controlled study involving the use of bovine colostrum for 1 week against placebo in preventing neutropenia among patientsundergoing chemotherapy. Participants were randomly assigned to receive the test products which were given orally 2x a day for 7 days starting simultaneously with the chemotherapy before the outcome measures were evaluated.*

Results: *A total of 21 subjects were enrolled, 10 of them received the placebo while 11 received the bovine colostrum. Results showed that there was significant increase in the Absolute Neutrophil Count (ANC) of patients given bovine colostrum as compared to the placebo group. There was also significant increase in the WBC and platelet counts among those who were given Bovine Colostrum. No incidence of infection or untoward effects on both treatment groups.*

Conclusion: *Bovine Colostrum is effective and safe in increasing the absolute neutrophil counts of ALL patients undergoing chemotherapy.*

Keywords: Neutropenia, All, Anc, Bovine Colostrum, Chemotherapy

Introduction

Children with cancer represent a unique population in the practice of pediatrics. Demise from cancer is not precisely due to cancer itself but from the complications associated with the disease and its treatment. Chemotherapy is the most common mode of treatment of pediatric cancer. The introduction of chemotherapy regimens has improved survival in children with cancer, but has increased the risk of infections.

Neutropenia is a common complication noted among cancer patients after chemotherapy. Chemotherapy-induced neutropenia typically occurs three to seven days after chemotherapy drugs are administered and continues for several days before recovering to normal levels [1]. The neutrophil count is important in predicting risk and response to infection and is measured in terms of an "absolute neutrophil count," or ANC. The normal range in healthy people for neutrophils is 2,500 to 6,000 per cubic millimeter of blood [2].

Neutropenic patients have an absolute neutrophil count (ANC) that is lower than 1,500 cells per microliter of blood. Neutropenia can be classified for patients greater than one year of age as mild, moderate and severe based on the ANC of 1,000 – 1,500, 500- 1,000, and < 500 cells per microliter of blood respectively [3]. As the absolute neutrophil count goes down, the patient's immunological status becomes compromised and the risk of infection rises correspondingly with the degree of neutropenia.

Treatment for neutropenia depends on the cause. In patients with impaired inflammatory response coupled with granulocytopenia, urgent empiric treatment with antibiotics of broad spectrum activity is warranted to decrease the risk of sepsis. For chemotherapy-induced neutropenia, the usual strategy in recent years has been theinjection with a man-made protein that is similar to the naturally occurring protein, which is the granulocyte-colony stimulating factor (G-CSF). G-CSF is produced in the body by the immune system and stimulates the formation of neutrophils [4]. These are usually given shortly after the last treatment in a chemotherapy cycle and are continued for up to two weeks, but their costs limit their use.

In cancer patients it has been suggested that fortification with good nutrition is the foundation for building a strong immune system. Although boosting the immune system is not the definitive treatment for cancer, this is incredibly important in the fightagainst cancer and infection. Colostrum has also been used successfully to help reverse neutropenia; at least on an anecdotal basis [2]. Bovine colostrum has shown some promise in different fields of medicine and has a lot of scope in the prevention and treatment of various illnesses including cancer in human beings. However, there is a need for double blind placebo-controlled multicentric trials to show scientifically its efficacy in real sense and more evidence is required before a firm conclusion can be made.

Objectives

The general objective of this study is to determine the efficacy of a 1 week supplementation of bovine colostrum (Pro-Ig) in preventing neutropenia among patients with acute lymphocytic leukemia (ALL) undergoing standard chemotherapy. The specific objectives are:1) To determine and compare the absolute neutrophil counts of patients among the study groups; 2) To determine and compare the incidence of anemia, leukopenia and thrombocytopenia between the study groups; 3) To evaluate the occurrence of clinically or culture proven infection and 4) To determine other untoward events or side effects on the use of bovine colostrum.

Significance of the Study

The purpose of this study is to determine whether bovine colostrum has a significant effect in preventing derangement on CBC values among patients receiving chemotherapy, thereby preventing the delays in the administration of chemotherapy and preventing infection in an immunocompromised patient. Results of this study may also contribute to the limited data on the use of Bovine Colustrum.

Review of Related Literature

Colostrum is a pre -milk substance, a thick lemon yellow mammary secretion produced after the birth of the newborn and lasts for 2-4 days. It supplies immune and growth factors and a perfect combination of vitamins and minerals to ensure the health, vitality and growth of the newborn [5]. This contains protective antibodies to prevent infection in the newborn called passive immunity.

Bovine colostrum is a milk secreted during the first few days after calving and and is a rich source of immunoglobulins and other antimicrobial factors. Laboratory analyses of immune and growth factors from bovine colostrum are similar to those found in human colostrums [6]. Even more important are reports that colostrum from cows is 4x richer in immune factors than human colostrum. These immunoglobulins are believed to improve the immune function and may be effective in treating immune system deficiencies and in the treatment of neutropenia. Cytokines found in colostrum namely the interleukins 1, 6, 10, interferon G and lymphokines have been the single most researched protocols in scientific research for the cure for cancer. Colostrum Lactalbumin and Latoferrin has been found to be able to cause the selective death of cancer cells, leaving the surrounding non-cancerous tissues [6].

A clinical research by Dr. David Tyrell, in England, in 1980, revealed that colostrum contains high percentage of antibodies and immunoglobulins which are believed not to be absorbed but remain in the intestinal tract where they attack organisms that causes diseasse before they penetrate the body. The remainder is believed to be absorbed and distributed in the body to assist in our internal defense processes. It is this combination of action that is believed to make colostrum so unique and effective as an oral supplement [7].

In a clinical study done in 2003 by Brikworth et al, it revealed that bovine colostrum supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males [8]. A similar local study done in a tertiary hospital in the Philippines in 2015 by Lesmana et al, revealed that bovine colostrum supplementation can be used as one effective adjunct therapy in reducing frequency of cough and cold in URTI as well as reducing frequency and amount of stool in AGE [9].

In a review of the clinical studies done by Struff etal, in 2008, it has been found that bovine colostrum was effective in infantile hemorrhagic diarrheas and it also reduced the likelihood of disease progressing to hemolytic uremic syndrome. It has also been tested in H pylori infection and diarrhea in immunodeficiency [10].

A clinical trial was done in 2010 by Panahi et al, using bovine colostrum in the management of children aged 1-10 years with nonorganic failure to thrive and it revealed that the group who received bovine colostrum had higher weight gain measured by both Waterlowe and Gomez Classification [11].

A local study was done in Manila, Philippines in 2013 by Jamarolin et al; using bovine colostrum in neonatal sepsis and it revealed that resolution of signs and symptoms like fever can be seen as early as 2 days from its administration [12].

Through hundreds of years of use and over 1000 clinical studies, colostrum has been demonstrated to be completely safe without drug interactions or side effects at any level of ingestion [7]. However, there have been rare reports of problems in HIV-positive patients such as nausea, vomiting, abnormal liverfunction tests, and decreased red blood cells [7].

There are limited data regarding the use of bovine colostrum and neutropenia and most are based on anecdoctal reports which are also inconsistent. Dr. Dwyer in 2011 in the New England Journal of Medicine claims that “Immunoglobulin in colostrum has been used to successfully treat Thrombocytopenia, Anemia, Neutropenia, and other conditions such as Myasthenia Gravis, Guillain Barre Syndrome, Multiple Sclerosis, Systemic Lupus, Rheumatoid Arthritis, Bulluos Pamphigoid, Kawasaki Syndrome, Chronic Fatigue Syndrome and Crohn’s disease”[6]. On the other hand, a FactMed analysis in 2012reported that 2 patients taking bovine colostrum developed neutropenia however this was not elaborated [13].

Materials and Methods

Study Design

Randomized, double-blind, placebo controlled trial.

Subjects

Pediatric patients aged 6 months to 18 years old diagnosed with ALL, and undergoing chemotherapy using the standard protocol and are on the maintanenace phase were invited to participate in the study. The study period was from February 2016 to September 2016.

Inclusion Criteria

1. An initial baseline WBC of more than or equal to 2.8 x 109/L 14provided that the absolute neutrophil count is more than or equal to 1000
2. An initial baseline Hemoglobin of at least 100 g/L and a platelet count of at least 150 x 10^9/L[15]
3. No other co-morbid illness like CHD, acute or chronic kidney disease and critical illness requiring admission at the intensive care unit and infection requiring antibiotic use.
4. No known allergy to dairy products.
5. Not presently taking other supplements/vitamins including bovine colostrum (Pro-Ig)
6. Either in-patient or outpatient

Sample Size Computation

Due to the limited number of ALL patients in this institution (2-4 cases of standard chemotherapy per month), sample size was determined by total enumeration wherein, all patients satisfying the inclusion criteria were included in the study period of 8 months.

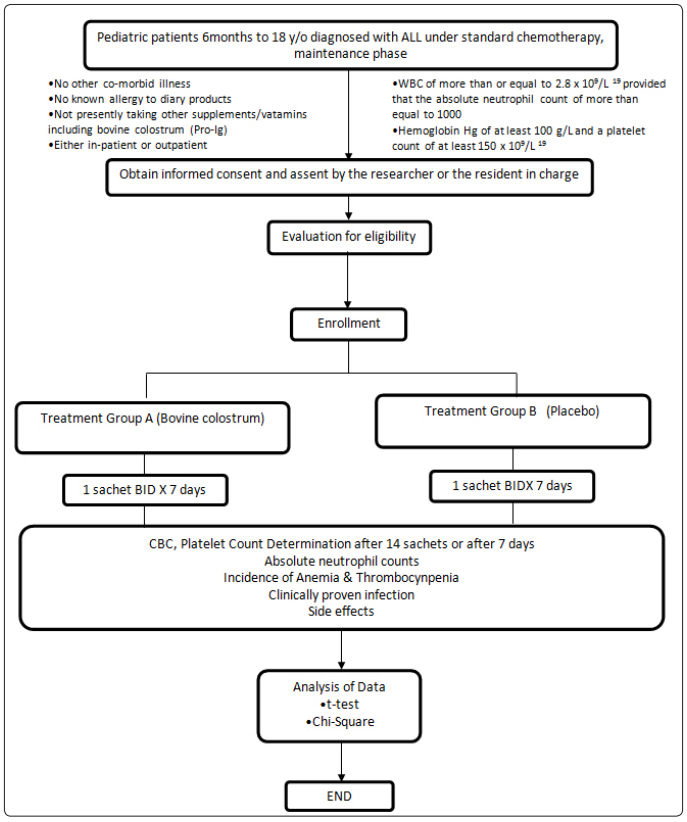
Methodology

Patients who were diagnosed with Acute Lymphocytic Leukemia fulfilling the inclusion criteria were recruited. Baseline CBC levelswere determined(from BGHMC Laboratory) and the absolute neutrophilic counts (ANC) were computed by multiplying the WBC counts with the neutrophils plus bands then the result is multiplied by 1000.Eligible participants were randomly assigned to either the treatment group or the placebo group. Assignment was done by simple randomization using the "fish bowl" technique wherein the parent or guardian picked a piece of paper from a box that contained the corresponding codes of the test products used.Each participant received either the bovine colostrum (Pro-Ig) or the placebo and wasblinded to the test article he/she received. The identity of the test products were only obtained& revealed from the supplier after the statistical analyses have been made.

Upon enrollment, the resident in charge gave the corresponding test product that was picked by the patient or parent. In the package an instruction, written in English, Tagalog and Ilokano, on the proper administration of the test product was placed. The instruction was also explained by the resident in charge. The test products were dissolved in 2 tablespoon of water until all the contents were dissolved and were given to the participants per orem twice a day for 7 days (after breakfast & after dinner) under the supervision of the nurse on duty/and or parent/guardian for in-patients and the guardian/parent/s for out-patients. The administration of the test products commenced on Day 1 of the standard chemotherapy and daily thereafter until 7 days, thereby completing 14 doses, before the outcomes were measured. The participants were also instructed not to discard the sachets after consuming and to give back allempty packages to the hematology-oncology resident after the 7 days treatment. The treatment regimen wasgiven prior to the administration of Vincristine.

After 7 days of treatment with the test article, a complete blood count and platelet countwererepeated at the BGHMC Laboratory only. Blood samples were extracted by the hematology oncology resident by drawing 0.5 ml of blood (if using aquisel microtainer tubes) or 2 ml of blood (if using EDTA tube) preferably in the antecubital area. The CBC& platelet count determinations were done at the Baguio General Hospital and Medical Center (BGHMC) Laboratory in accordance with their test protocol/standard operating procedures.

Schematic Diagram and Description of the Study Procedure



Statistical Analysis

Frequency and percentage were used to describe the demographic data. Fisher's exact testwas used to determine significant differences in the distribution proportion between treatment groups.The primary outcome measure (ANC) and various CBC parameters for each treatment group were computed and analyzed using Levene's test for equality of variances to determine whether there are significant differences between the treatment groups before interventions were given. Dependent T-test was applied to determine significant differences before and after the treatment on each group and an independent t-test in comparing primary outcome measure between the two groups.

Results

Table 1 : Demographical Profile as to age and sex and Pretreatment CBC, ANC, & platelet Count valuesof ALL Patients undergoing Standard chemotherapy in Baguio General Hospital and Medical Center in February 2016 to September 2016 (N=21)

PARAMETERS	Placebo Group (n=10)	BovineColostrum Group (n=11)	p-value*
a. Age			
1 – 9 y/o	8 (38.1%)	10 (47.6%)	0.586
10& above	2 (9.5%)	1 (4.8%)	
b. Sex			
Male	6 (28.6%)	8 (38.1%)	0.659
Female	4 (19.0%)	3 (14.3%)	
CBC, ANC & Platelet Count**			
Hemoglobin(g/L)	128.30	146.10	0.992
Hematocrit (%)	0.38	0.44	0.472
WBC (x10^9/L)	6.00	5.68	0.307
Neutrophils (%)	0.70	0.61	0.974
Lymphocytes (%)	0.26	0.40	0.681
Monocytes (%)	0.03	0.02	0.405
Eosinophils (%)	0.02	0.04	0.066
Platelet Count (x 10^9/L)	382.50	316.10	0.924
ANC	4215.49	3189.31	0.304

*significant @ p-value < 0.05
**expressed as mean values

Table 1 shows the age-sex distributionand baseline parameters of patients diagnosed with ALL undergoing standard chemotherapy. Majority in the placebo and treatment group belonged to the age group of 1-9 yrs old at 38.1% and 47.6% respectively. Most cases were also male at 28.6% and 38.1% in both treatment groups. There was no significant difference on the demographics of both treatment groups as indicated by the p value of 0.659 and 0.586 for gender and age respectively.

In comparing the variances in the baseline characteristics, considering CBC, ANC and platelet counts of patients, Levene's test of equality of variances was applied.There is no significant difference in the pretreatment CBC, ANC, & platelet Count valuesof both treatment groups as shown by the p values of more than 0.05, indicating that the population is homogenous.

Table 2: Pre and Post Treatment CBC, ANC, & platelet Count values of ALL Patients undergoing the Maintenance Phase of the Standard Protocol under the Placebo Group (n=10)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		p*
			mean	%	
CBC, ANC & Platelet Count**					
Hemoglobin(g/L)	128.30	125.20	-3.1	-2.42%	0.225
Hematocrit (%)	0.38	0.37	-0.01	-2.63	0.290
WBC (x10^9/L)	6.00	5.63	-0.37	-6.17	0.555
Neutrophils (%)	0.69	0.60	-0.09	-13.04	0.045*
Lymphocytes (%)	0.26	0.31	0.05	19.23	0.098
Monocytes (%)	0.027	0.024	-0.003	-11.11	0.771
Eosinophils (%)	0.019	0.051	0.032	168.42	0.045*
Platelet Count (x10^9/L)	382.50	407.6	25.1	6.56	0.269
ANC	4,215.50	3,406.96	-808.54	-19.18	0.167

*significant @ p-value < 0.05
**expressed as mean values

Table 2 shows the comparison of pre and post treatment CBC, ANC and platelet count values of patients under the placebo group. Based on the results, it shows that the CBC results on hemoglobin, hematocrit, WBC, neutrophils, ANCdecreased after chemotherapy however, only the neutrophils significantly decreased as shown by the p-value that is less than 0.05. It is also observed that there are no significant increase on CBCparameters like lymphocytes, monocytes and platelet count except for eosinophils which increased significantly.

Table 3: Pre and Post Treatment CBC, ANC, & platelet Count of ALL Patients undergoing the Maintenance Phase of the Standard Protocol under the Bovine Colostrum Group (n=11)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		P
			mean	%	
CBC, ANC & Platelet Count*					
Hemoglobin(g/L)	132.82	120.27	-12.55	-9.45%	0.007*
Hematocrit (%)	0.397	0.36	-0.037	-9.32%	0.003*
WBC (x10^9/L)	5.162	7.43	2.268	44.19%	<0.001*
Neutrophils (%)	0.55	0.63	0.08	14.55	0.176
Lymphocytes (%)	0.36	0.32	-0.04	-11.11	0.355
Monocytes (%)	0.021	0.024	0.003	14.29	0.71
Eosinophils (%)	0.038	0.032	-0.006	-15.79	0.476
Platelet Count (x10^9/L)	287.36	378.09	90.73	31.57	0.001*
ANC	2899.37	4561.19	1661.82	57.32	0.007*

*significant @ p-value < 0.05
**expressed as mean values

Table 3 shows the comparison of pre and post treatment CBC, ANC and platelet count values of patients under the Bovine Colostrum group. Based on the results, it shows that the hemoglobin and hematocrit decreased significantly with p-values of 0.007 and 0.003 respectively. It was also observed that the lymphocytes of the patients decreasedafter treatment but this was not significant. There was also increase on the neutrophils and monocytes of the patients but only minimal. The WBC, ANC and Platelet counts increased significantly after the administration of Bovine Colustrum with p-values of<0.001, 0.001 and 0.007 respectively.

Table 4: Mean Changes in the CBC, platelet Count and ANC Values of ALL Patients undergoing the maintenance Phase of the Standard Protocol for both Study Groups (N=21)

Variables	Placebo Group			Bovine Colostrum Group			p
	Pre Tx	Post Tx	Mean Δ %	Pre Tx	Post Tx	Mean Δ %	
CBC, ANC & Platelet Count*							
Hemoglobin(g/L)	128.30	125.20	-3.1	132.82	120.27	-12.55	0.051
Hematocrit (%)	0.38	0.37	-0.01	0.397	0.36	-0.037	0.020*
WBC (x10^9/L)	6.00	5.63	-0.37	5.162	7.43	2.268	0.002*
Neutrophils (%)	0.69	0.60	-0.09	0.55	0.63	0.08	0.021*
Lymphocytes (%)	0.26	0.31	0.05	0.36	0.32	-0.04	0.099
Monocytes (%)	0.027	0.024	-0.003	0.021	0.024	0.003	0.644
Eosinophils (%)	0.019	0.051	0.032	0.038	0.032	-0.006	0.027*
Platelet Count (x 10^9/L)	382.50	407.6	25.1	287.36	378.09	90.73	0.041*
ANC	4,215.50	3,406.96	-808.54	2899.37	4561.19	1661.82	0.003*

*significant @ p-value < 0.05
**expressed as mean values
Tx: treatment

Table 4 shows the comparison on the mean changes in the pre-treatment CBC, ANC and platelet count values of both treatment groups'patients after the intervention. The result shows that there is a significant decrease in the hematocrit of patients that were given the drug Bovine Colostrum as compared to those patients that were given placebo. Although the decrease in the hemoglobin values was higher among the Bovine Colostrum group as compared to the placebo group, this was not significant. The WBC and neutrophil values decreased among the placebo group with a mean decrease of 0.37 and 0.39 respectively while it increased in the Bovine Colostrum group with a mean of 2.268 and 0.08 respectively, indicating a favorable effect of Bovine Colostrum. The lymphocyte counts of both groups after the intervention changed in opposite direction with a mean increase of 0.05 among the placebo group and a mean decrease of 0.04 amonth the Bovine Colustrum group however this difference was not significant. The monocyte values also changed on opposite trends with a mean decrease of 0.003 on the placebo group and a mean increase of 0.003 on the Boveine Colostrum group but this was not also significant. The eosinophil values increased among the placebo group at a mean of 0.032 while it decreased at 0.006 among the Bovine Colostrum group however this was not significant. Platelet Count and ANC values increased in both groups however the mean increase among the Bovine Colostrum group was significantly higher at 90.73 and1661.82 respectively.

Adverse Effects

There was no noted clinically or proven infection in both treatment groups. Likewise, no untoward event or side effect was observed during and after the intervention.

Discussion

Acute lymphoblastic leukemia (ALL) or cancer of the white blood cells, is characterized by the overproduction and accumulation of cancerous, immature white blood cells, known as lymphoblasts. It is most common in childhood, with a peak incidence at 2–5 years of age and slightly more common in males than in females and the reason for this is still unknown [16]. Risk classification (such as standard-risk, high-risk, or very high-risk) is based on the age at diagnosis and initial white blood cell count with more intensive treatment given to higher risk patients. Children between the ages of 1 and 9 with B-cell ALL are considered low risk and tend to have better cure rates. Children younger than 1 year and those 10 years or older are considered high-risk patients. Moreover, children with ALL who have very high WBC counts (greater than 50,000 cells per cubic millimeter) when they are diagnosed are classified as high risk and need more intensive treatment [17].

Standard chemotherapy or protocol for ALL consists of three phases: remission induction, intensification (consolidation), and maintenance therapy along with CNS prophylaxis. In Remission induction phase, the aim is to rapidly kill most tumor cells. Remission is defined as the presence of less than 5% leukemic blasts in the bone marrow, normal blood cells and absence of tumor cells from blood, and absence of other signs and symptoms of the disease. Central nervous system (CNS) prophylaxis should begin during this phase of treatment and continue during the consolidation/intensification period. A combination of prednisolone or dexamethasone, vincristine, asparaginase is used to induce remission which is given over 4-6 wk. Consolidation/intensification phase uses high doses of intravenous multidrug chemotherapy to further reduce tumor burden [17].

Maintenance therapy is intended to kill any residual cell that was not killed by remission induction and intensification regimens. Daily oral mercaptopurineat 40-50mg/m^2, once weekly oral methotrexate at 15-20 mg/m^2, once monthly 5-day course of intravenous vincristine at 1.5mg/m^2 dose and oral corticosteroids at 15-20 mg/m^2 PO are

usually used to be given in 36 months [17].

The bovine colostrum (Pro-Ig) that was used in this study is in a granulated powder produced via thermisation treatment, from a reputable company in France. It also contains food additive such as silicon dioxide and dextrose monohydrate. The only contraindication of this product is hypersensitivity to any component of the product. However, according to Dr. Keech, individuals who are lactose intolerant can easily tolerate up to 12 grams of colostrum per day without any negative side effects or symptoms.The proline-rich polypeptide in colostrum normalizes or modulates the levels of cytokines in the body, so the body does not recognize the lactose as a food allergen in cases of lactose intolerance [7]. Participants in this research were given 2 grams of colostrum per day. On the other hand, the placebo used contains pea starch.

In this study, all patients enrolled were in themaintenance phase of chemotherapy inorder to standardize the research.Majority (85.71%) of the subjects were on the age 1-9 years age group and 66.7% were males. Treatment groups were homogenous as there was no significant difference on the demographics and baseline parameters before the intervention was given.

Therewerefew significant changes noted on the study variables in the placebo group involving theneutrophil and eosinophil counts which decreased and increased respectively. The decrease in the neutrophil count may still be attributed to the chemotherapy given. Neutropenia is a common complication noted among cancer patients after chemotherapy.The increase however in the eosinophilic count remains to be elucidated since this is not a usual response to chemotherapy. Although increase in eosinophils is commonly seen among patients with hypersensitivity and parasitic infestations, there were no clinical manifestations of these conditions among the group.

The administration of bovine colostrumduring chemotherapy showed some promising effects on theWBC, platelet and ANCof patients undergoing chemotherapy as noted in this study. After the intervention, there was a striking change on the values of WBC, neutrophils, monocytes and ANC among the Bovine Colustrum group in which all of these parameters increased significantly while their values have all decreased among the placebo group. The increase in neutrophils as noted in this study refutes the finding of neutropenia on 2 patients given colostrum as reported in a FactMed analysis in 2012 [13]. Although the trend of change on the platelet counts was similar on treatment groups, the mean increase in the platelet counts of those given Bovine Colostrum was significantly higher than the placebo group. These favorable effects of Bovine Colustrum are quite promising since these effects are not usually observed after administration of chemotherapeutic agents. The noted decrease in both hemoglobin and hematocrit may still be due to chemotherapy itself but the significantly lower hematocrit observed in the Bovine Colostrum group but its clinical significance needs more validation since no patient among the Bovine Colustrum group required transfusion.

Tha scarcity of published data on the effects of Bovine Colustrum on blood parameters especially CBC, ANC and platelet counts makes it difficult to conclude that such beneficial effects are directly due to Bovine Colustrum. The beneficial effects noted here however indirectly supports the findings of previously mentioned studies that colostrum enhances the effect of immunoglobulins, decreases signs and symptoms of upper respiratory tract infection, diarrhea, and sepsis as claimed by Tyrell, Lesmana et al, Struff et al, and Jamaroli et al respectively on their studies.

Conclusion

This study shows that Bovine Colostrum is effective and safe in preventing leukopenia, neutropenia and thrombocytopenia among ALL patients undergoing chemotherapy thereby preventing delays in chemotherapy.

Study Limitations

The major limitation of this study lies on its small sample size due to the limited number of patients using the standard protocol. This adversely affects the power of the study.

Recommendations

This study was done with a small population hence further studies with bigger population is encouraged in order to validate the results of this study. Investigations on the effect of Bovine Colostrum on other forms of cancer is likewise a good endeavor to evaluate whether effects are similar.

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Appendices

A. Summative Collecction Form of Pretreatment and Post treatment CBC, ANC, & platelet Count values of ALL Patients undergoing the Maintenance Phase of the Standard Protocol under the Placebo Group (n=10)

Participant number	Age	Sex	Address	Phase of chemo	Hgb	Hct	WBC	Neutrophils	Lymphocytes	Monocyte	Eosinophils	Platelet	ANC	Side Effects
1.	4	F	Pangasinan	Maintenance	136	0.4	8.0	0.77	0.20		0.02	570	6160	None
					133	0.4	4.5	0.76	0.24			550	3420	None
2	3	M	Pangasinan	Maintenance	115	0.35	6.13	0.9	0.09	0.01		391	5517	None
					126	0.37	5.54	0.54	0.39	0.03	0.04	425	2991.6	None
3.	5	F	Pangasinan	Maintenance	112	0.33	8.5	0.8	0.17			277	6800	None
					106	0.31	4.39	0.58	0.29	0.01	0.12	252	2546	None
4.	7	M	Baguio City	Maintenance	120	0.34	6.69	0.57	0.32	0.08	0.03	482	3813.3	None
					124	0.35	6.7	0.62	0.3	0.02	0.04	598	4154	None
5	11	F	Mt. Province	Maintenance	128	0.41	4.16	0.72	0.24		0.04	238	2995.2	None
					131	0.38	5.3	0.62	0.29	0.01	0.03	268	3286	None
6.	4	M	Benguet	Maintenance	150	0.43	4.75	0.65	0.30	0.05		456	3087.5	None
					143	0.41	5.38	0.56	0.31	0.04	0.09	363	3012.8	None
7.	4	M	Pangasinan	Maintenance	116	0.34	6.14	0.54	0.42		0.03	377	3315.6	None
					112	0.37	7.37	0.49	0.43	0.02	0.06	495	3611.3	None
8.	4	M	Pangasinan	Maintenance	128	0.37	5.98	0.83	0.15		0.02	417	4963.4	None
					114	0.35	7.04	0.77	0.16	0.03	0.04	484	5420.8	None
9.	12	F	Ifugao	Maintenance	153	0.45	4.81	0.75	0.16	0.06	0.03	314	3607.5	None
					141	0.41	5.24	0.73	0.16	0.16	0.03	285	3825.2	None
10.	5	M	La Union	Maintenance	125	0.37	4.86	0.39	0.50	0.07	0.02	303	1895.4	None
					122	0.36	4.87	0.37	0.53	0.01	0.06	356	1801.9	None

B. Summative Collecction Form of Pretreatment and Post treatment CBC, ANC, & platelet Count values of ALL Patients undergoing the Maintenance Phase of the Standard Protocol under the Bovine Colostrum Group (n=11)

Participant number	Age	Sex	Address	Phase of chemo	Hgb	Hct	WBC	Neutrophils	Lymphocytes	Monocyte	Eosinophils	Platelet	ANC	Side Effects
1	3	M	Benguet	Maintenance	119	0.36	7	0.59	0.35	0.01	0.05	306	4130	None
					108	0.31	8.97	0.47	0.47		0.06	428	4215.9	None
2.	5	M	Pangasinan	Maintenance	125	0.37	4.48	0.46	0.39	0.04	0.01	323	2060.8	None
					115	0.34	6.84	0.5	0.44	0.02	0.04	488	3420	None
3.	6	M	Baguio city	Maintenance	168	0.50	2.23	0.68	0.24	0.01	0.03	202	1516.4	None
					127	0.38	3.6	0.59	0.33	0.04	0.04	306	2124	None
4.	4.	M	Itogon	Maintenance	124	0.39	4	0.3	0.67	0.01		200	1200	None
					122	0.36	0.36	0.76	0.23	0.01		314	7166.8	None
5.	4	M	La Trinidad	Maintenance	133	0.39	2.8	0.69	0.26		0.02	190	1932	None
					110	0.32	5.71	0.8	0.13	0.05	0.02	254	4568	None
6.	6	F	Pangasinan	Maintenance	125	0.37	6.11	0.58	0.30	0.03	0.07	262	3543.8	3543.8
					123	0.37	6.33	0.78	0.21	0.01		214	4937.4	None
7.	5	F	Apayao	Maintenance	127	0.39	6.16	0.36	0.56	0.02	0.04	412	2217.6	None
					115	0.35	9.85	0.32	0.61	0.02	0.03	505	3152	None
8.	7	M	Nueva Ecija	Maintenance	131	0.38	3.84	0.52	0.43	0.01	0.03	279	1996.8	None
					128	0.37	6.36	0.7	0.23	0.02	0.05	336	4452	None
9.	11	M	Benguet	Maintenance	147	0.44	6.11	0.69	0.21	0.03	0.05	305	4215.9	None
					141	0.41	6.82	0.74	0.19	0.05	0.01	343	5046.8	None
10.	5	M	Pangasinan	Maintenance	143	0.40	5.18	0.45	0.42	0.01	0.12	404	2331	None
					118	0.35	7.61	0.52	0.37	0.01	0.1	473	3957.2	None

11	2	F	Pangasinan	Maintenance	119	0.38	8.88	0.76	0.17	0.06		278	6748.8	None
					116	0.37	10.19	0.7	0.26	0.03		498	7133	None

C. Informed consent form (english version)

Research Title: The Effect of Bovine Colostrum on the Absolute Neutrophil Count of Pediatric Patients with Acute Lymphocytic Leukemia undergoing Chemotherapy - A Double Blind Randomized Placebo Controlled Study

Principal Investigator: Edith Cyrill L. Caysido, MD
Pediatric Resident
BGHMC Department of Pediatrics

Part I: Information Sheet

Introduction

Good day! I am Edith Cyrill L. Caysido, M.D., a Pediatric Resident of Baguio General Hospital and Medical Center. I am conducting a study with the title: "The Effect of Bovine Colostrum on the Absolute Neutrophil Count of Pediatric Patients with Acute Lymphocytic Leukemia undergoing Chemotherapy - A Double Blind Randomized Placebo Controlled Study" and I am inviting your child to be a part of this study.

Neutropenia is a common side effect of chemotherapy in cancer patients. Neutropenia is defined as a low number of neutrophil granulocytes, a type of white blood cell, in the body. White blood cells serve as the body's primary defense mechanism against infection and disease. Therefore, patients with neutropenia are more susceptible to disease and infection. Severe cases of neutropenia may even become life threatening.The purpose of this research is to see the effect of the bovine colostrum in preventing neutropenia in patients undergoing chemotherapy.

Every patient will be assigned to a group by using the "fish bowl" technique wherein the parent or guardian shall pick a piece of paper from a box that contains the corresponding code of the test product to be used. Each participant will receive either the bovine colostrum (Pro-Ig) or the placebo (the drug with no active ingredient). In each of the package that was picked contains an instructional guide written in English, Tagalog and Ilokano on how to prepare the test product. The test products are given orally 2x a day after breakfast and after dinner starting simultaneously with the chemotherapy and continued for 7 days before the outcome measures are evaluated. The progress of your child will be carefully monitored at regular intervals.

I am inviting your child to participate in this research because it is important that we confirm the efficacy of this new and cost-effective treatment option. Your child is chosen to be a part of this research since he/she fulfills the selection criteria ideal for this study.

Voluntary Participation

Your decision to have your child participate in this study is entirely voluntary. Whether you decide to join or not, the treatment of your child will not be affected. All the services you and your child receive in this hospital will continue and nothing will change. You may also choose to change your mind later and stop participating, even if you agreed earlier, and the services you and your child receives in this hospital will continue.

Information on the Trial Drug

Bovine Colostrum (Pro-Ig) is colostrum extracted from a cow. It has similar composition with that of human colostrum. This colostrum has been treated and sterilized so that it would be fit for humans' consumption. The bovine colostrum (Pro-Ig) that we will be using has no known side effects based on literature.

The placebo pertains to the drug with no active ingredient. This contains pea starch or flour that is palatable. It is safe for neonates, infants and children.

Procedures and Protocol

It has not been established if bovine colostrum can really improve your child's WBC count with chemotherapy. We want to see how efficient it is to prevent the marked decrease of WBC count after chemotherapy that's why we are asking your consent to allow your child to participate. Children who will take part in this research will be assigned into groups which are to be selected by chance. One group will get the bovine colostrum (Pro-Ig) that we are testing, and the other group will get the placebo (the drug with no active ingredient).

The funding for this research study will come from the research fund of Baguio General Hospital and Medical Center and you will not be required to pay additional charges in your hospital bill if you decide to participate in this study.

Duration

The study period will be from October 2015 to April 2016. All in patients or out patients diagnosed with Acute Lymphocytic Leukemia undergoing standard chemotherapy during this period who qualifies for the study will be invited to participate.

Risks, Discomforts and Side effects

There are no known major side effects from bovine colostrum (Pro-Ig) or placebo (the drug with no active ingredient). Any untoward reaction from the drug will be carefully monitored and appropriate management will be given by the hematology oncology rotator.

Benefits

Your child's participation in this study will help us answer the research question in the management of neutropenia in patients with Acute Lymphocytic Leukemia following chemotherapy. Patients with Acute Lymphocytic Leukemia will greatly benefit from the outcome of this study if results will be promising.

Confidentiality

The information that we will collect from this research project will be kept confidential. Any information about your child will have a number on it instead of his/her name. Information about your child that will be collected from the research will be kept for a period of 2 years and no one but the researchers will be able to see it. Research data will be discarded after this period by placing it in research archives.

Sharing of the results

At the end of the study period, the results will be processed and analyzed. We also intend to publish the results so that those who

are interested about this topic may learn and benefit from this study as well.

Right to Refuse or Withdraw

Should you refuse to allow your child to participate in this study; such decision will not affect the treatment of your child in this center in any way. You and your child will receive the benefits that you would otherwise have at this center.

Alternatives to Participating

If you do not wish your child to participate in this study, your child will be given the standard form of treatment.

Whom to Contact

If you have any questions, concerns or complaints regarding this research, you may contact me through this cellphone number-09257999333 Or, you can see me at the Baguio General Hospital and Medical Center, Department of Pediatrics conference room, 2nd floor, BGHMC Flavier building. The landline to the conference room is 444 8299. I will be glad to answer any of your queries.

If you have any questions or concerns regarding your child's rights as a research participant, you may also contact the BGHMC Ethics Review Committee chairman – Dr. Frederick Mars Untalan at the BGHMC Training Office. The said office is open from 8AM to 5PM from Monday to Friday. The ERC secretary, Ms. Joy Bautista, can also be reached through this landline number 444 2169, if in case anyone from the research staff is not around.

Part II: Certificate of Consent

I have been invited to have my child participate in the study on the effect of bovine colostrum in the absolute neutrophil count of patient with Acute Lymphocytic Leukemia undergoing chemotherapy. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study.
Print Name of Participant: _____

Print Name of Parent or Guardian: _____

Signature of Parent or Guardian: _____

Date: _____

If illiterate…

I have witnessed the accurate reading of the consent form to the parent of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.
Print Name of Witness: _____

Thumb Print of Parent:

Signature of Witness: _____

Date: _____

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the parent of the potential participant, and to the best of my ability made sure that the person understands what is stated in this consent form.

I confirm that the parent was given an opportunity to ask questions about the study, and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this informed consent form has been provided to the participant.

Print Name of Researcher/Person Taking the Consent:
_____

Signature of Researcher/ Person Taking the Consent:
_____

Date: _____

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