Acute Toxicity of Chemotherapeutic Agents Used For Treatment of Patients with Malignancy in kerbala Province/Iraq

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Abstract

Background: the number of cancer cases increasing not only in adult patients but also during childhood overall the world. Treatment with chemotherapy differs according to the case and type of cancer. Some of these systems produce toxic effects especially for the children which may be dangerous or even fatal. So that, studying these toxicities and adverse effects may help in improving patient outcomes and survive their life.

Objective: to investigate the most common acute adverse effects of cancer patients undergoing cytotoxic chemotherapy.

Methodology: sixty one (61) patients diagnosed with different types of cancer were enrolled in this study (39 males and 22 females) in the Oncology center, Pediatric Department/ Imam Hussein hospital of Kerbala/Iraq. The age of them was from 7 months to 17 years. Types of cancers were classified according to the histopathological features and clinical diagnosis and classified according to the affected organ. Venous blood was taken from each patient at morning before taken the drug for further investigations such as complete blood count and biochemical assay.

Results: mean ± stander error for weight of male (20±1.71) and for female (18.86±1.80), and the age of patients was (7months-17years). The cases where distributed as 56.45% of cases were in urban area and 41.53 % in rural area. 76.57% of patients were poor, while 26.31 % were middle and 15.78% were classified as rich patients. Significant differences were observed in types of cancers between male and female patients ($p \leq 0.05$). In addition, the effect of chemotherapy was clear on the number of White Blood Cells (WBC) since etoposide and cytosar have no effect on WBC number other than drugs. While drugs have non-significant effect on hemoglobin concentration. Effect of vincristine and Leucovorine drugs led to a significant decrease in the number of blood platelets. Effect on renal function markers also were examined and the urea and creatinine were affected largely by the interactions between the drugs.

Conclusion: patients who are diagnosed with cancer may lose their life not only by cancer disease, but may because of the treatment by chemotherapy drugs systems since some interactions between these drugs may be fatal in addition to their toxicities. There for, choosing correct drugs with correct doses have a large role to save their life.

Keywords: cancer, chemotherapy, acute toxicities, drug interactions.

تقييم السمية الحادة لادوية العلاج الكيميائي المستخدم لعلاج المرضى المصابين بالاورام الخبيثة في محافظة كربلاء/العراق

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الخلاصة

الخلفية: مع مرور الوقت ، ازدادت عدد حالات السرطان ليس فقط لدى المرضى البالغين وحتى خلال مرحلة الطفولة في جميع أنحاء العالم. تختلف أنظمة العلاج الكيميائي وفقًا لحالة ونوع السرطان حيث ان بعضا من هذه الأنظمة تنتج تأثيرات سامة خاصة على الأطفال والتي قد تكون خطيرة أو حتى مميتة لذا ، فإن دراسة التأثيرات السلبية للدوية الكيمياوية قد تساعد في تحسين نتائج المرضى والبقاء على قيد الحياة.

الهدف: التحقق من الآثار الضارة الحادة الأكثر شيوعًا لمرضى السرطان الخاضعين لأنظمة العلاج الكيميائي وتاثيراتها السمية على الخلايا.

المنهجية: سجل واحد وستون (61) مريضا تم تشخيصهم بأنواع مختلفة من السرطان وبواقع (39 ذكور و 22 إناث) في مركز الأورام ، قسم الأطفال / مستشفى الإمام الحسين التعليمي في كربلاء / العراق. تراوحت اعمار المرضى من 7 سبعة أشهر إلى 17 سبعة عشر سنة. صنفت أنواع السرطانات بالاعتماد على السمات النسيجية المرضية والتشخيص السريري والعضو المصاب. سحبت عينه الدم الوريدي من كل مريض في الصباح قبل أعطاء الدواء لاجراء عدة فحوصات مختبرية كاحتساب عدد كريات الدم الكامل والمقايسة البيوكيميائية.

النتائج: تم احتساب المتوسط ± الخطأ المعياري لوزن الذكور (20 ± 1.71) وللأناث (18.86 ± 1.80) ، وكان عمر المرضى من (7 أشهر - 17 سنة). وزعت الحالات حيث كانت نسبة 56.45٪ من الحالات في المناطق الحضرية و 41.53٪ في المناطق الريفية. اما الحالة المعيشية كانت نسبة 76.57٪ من المرضى ضمن الفئة الفقيرة، و نسبة 26.31٪ كانوا من العوائل متوسطة الدخل بينما 15.78٪ صنفوا كمرضى أغنياء. وجد هنالك اختلاف معنوي عند مستوى احتمالية ($P\leq0.05$) في انواع السرطانات بين الذكور والاناث. كما ان للعلاج الكيميائي تاثير معنوي في انخفاض عدد كريات الدم البيضاء على الرغم من ان عقاري الايتوبوسيد و سايتوسار لم يظهرا اي تأثير على عدد كريات الدم البيضاء . لم يظهر تأثير منفرد معنوي للأدوية على تركيز الهيموجلوبين. بينما أدى تأثير عقاري فينكريستين وليوكوفورين إلى انخفاض ملحوظ في عدد الصفائح الدموية. فحصت معايير وظائف الكلى وكان هنالك تأثير واضح إلى حد كبير لليوريا والكرياتينين بالتداخلات العلاجية للادوية الكيمياوية.

الأستنتاج: الأطفال الذين تم تشخيص إصابتهم بالسرطان قد يفقدون حياتهم ليس فقط بسبب أمراض السرطان ، وربما بسبب أنظمة العلاج المعطاة لمريض السرطان وقد تسبب بعض التفاعلات بين هذه الأدوية الكيمياوية تاثيرات سمية قاتلة وعليه فأن اختيار الانظمة العلاجية المناسبة قد تقلل من هذه التأثيرات.

Introduction

Cancer is a broad meaning word, it includes a wide variety of tumor types. In general, cancer mean uncontrolled cell growth and proliferation. Normal cell could be transformed to cancerous cell by mutation or other genetic causes resulting in loosing normal cell cycle. Cancer cells are characterized by their ability to invade surrounding tissue and migration to other organs. Molecular analysis and genomic tests showed that there are diversity of cancer types arises from number of signaling pathway. These are related to endogenous and exogenous factors (1). In developed countries, invasive cancers is reported as the leading cause of deaths and the second cause of deaths in developing countries(2) approximately, 12.7 million people were diagnosed with invasive cancers in 2008 and in 2010,about 7.98 deaths which accounts 16% of deaths at this time (3). The most common types of cancers which are reported in 2018 were lung cancers (1.76 million deaths), colorectal cancers (860000), and breast cancers (620,000). This makes invasive cancer the leading cause of death in the developed world and the second leading in the developing world. Several types of cancer could be developed during childhood such as carcinoma, thyroid cancer arises from

Hashimotos thyroiditis, Hodgkin and non-Hodgkin lymphomas (4) , Leukemia , Brain and spinal cord tumors , Neuroblastoma , Wilms tumor, Rhabdomyosarcoma, Retinoblastoma , Bone cancer (including osteosarcoma and Ewing sarcoma).the survival percent of cancers in children in developed countries is usually better than in developing countries. Also, in low and middle income countries 80% of world's children live but, 56% of the cases and 64% of the deaths occur each year due to limited access to curative treatment including the lack of availability of common chemotherapeutic agents, cost of treatment, late stage at presentation, and limited radiotherapy and surgical resources. In addition, even when adequate oncologic treatments are available, differences in education level and socioeconomic status, coupled with in efficient care delivery resulting in poor patient outcome in middle and low income countries(5).

Chemotherapy (CTX or CTx) is a type of drugs used to treat cancers called chemotherapeutic agents. It is usually given in combination (or sometimes one type) to produce maximal effect. It is used with specific regimen depending on cancer type and patient status. Also, chemotherapeutic agents are used with surgical and radiological therapy. Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called medical oncology (6). Cancers are usually treated either by surgical operation followed by courses of chemotherapy agent or by chemotherapy alone in addition to the newly developed techniques. Chemotherapeutic techniques have a range of side-effects that depend on the type of medications used. The most common medications affect mainly the fast-dividing cells of the body, such as blood cells and cells lining the mouth, stomach, and intestines. Chemotherapy adverse effects and toxicities can occur immediately after administration, within hours or days, or chronically, from weeks to years (7). These include Neutropen enterocolitis, Gastrointestinal distress, Anemia, Nausea and vomiting, and fatigue (8, 9).

Patients and methods

Patients: Sixty one (61) cancers patients, thirty nine 39 (63.9 %) were males and twenty two 22 (36.1%) females are enrolled in the present study, mean ± standard error for weight of males (20.39 ± 1.71) and for females (18.86 ± 1.80). The age of patients was range from (7 months-17 years).The major patients were recruited from Oncology Center (IAOC) Pediatric Department /Imam Hussain Hospital, Kerbala/Iraq, during August– November 2019-. All patients diagnosed with presumed malignancies- diagnosis according to the World Health Organization (WHO) classification of tumors. Administrative and ethical approval and consent was obtained from the scientific committee of pharmacology department/collage of pharmacy in Kerbala University, with agreement of IAOC staff and administrator. Patient's data and names kept strictly confidential and used for scientific research purposes only. A specifically designed questionnaire used together information that contained many questions. Identification of specific questions through reviewing a literature on patient's malignancies. The measurement of body weights by body balance and height, by paper tape to calculate body surface area for the purpose of calculating the therapeutic dose according to the body surface area of the patient. Cancer types were classified according to histopathological features and clinical diagnosis, and categorized according to organ involvement into anatomical systems. The types of cancer under study are: Non hodgkin lymphoma, Hodgkin lymphoma, Acute lymphoblastic leukemia (ALL), Rhabdomyosarcoma (RMS), Neuroblastoma and Osteosarcoma.

Methods:

1. Complete blood count method

At morning before the chemotherapy administration, five [5] ml of blood samples was taken from the patients vein by using a disposable needle and plastic syringes , blood collected put in EDTA tube and then put in Sysmex instrument to determine the CBC by Germany hematocrit (10).

2. Biochemical assay method

Creatinine and blood urea nitrogen are The major biochemical tests to detect kidney function, five [5] ml of venous blood samples were drown using a disposable needle and plastic syringes from patients, blood sample were mainly collected in gel tube and centrifuged at 3000 rpm for 10 minutes to get serum for analysis (11).

3. Statistical Analysis

Data was analyzed by using SPSS program version. The results were computed as mean ± standard error or percentage (%), data were analyzed by two- way (ANOVA) test was used for the comparison between the types of cancer and one- way (ANOVA) test was used for the comparison between the different study data. The P values of difference ≤ 0.05 were considered as statistically significant (12).

Results

First of all, it was important to compare the percentage of cancer occurrence in the rural and urban areas to highlight the causes of the increasing number of cancer cases. Find out the disposing factors such as environmental and behavioral causes help the specialists to making strategies in attempts to save people and prevent this harmful disorder especially during childhood. Figure 1 explain the percentage of cancer cases in both areas:

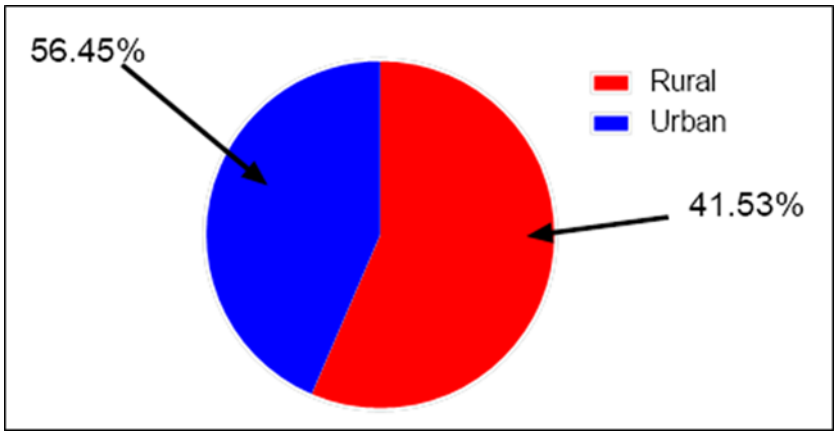

Figure 1: Distribution of cancers patients in kerbala governorate according to rural and urban area.

Similarly, the differences in the number of cancer cases between males and females were examined in this study because sex is important factor to be studied in this types of diseases which may result from hormonal or other sexual related causes as showed in figure 1.

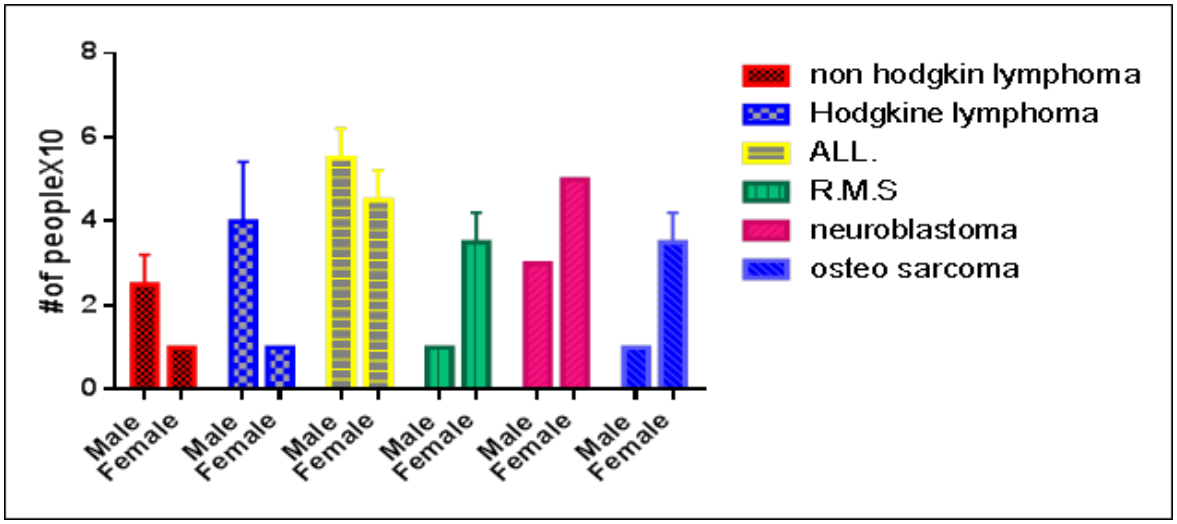

Figure 2. Susceptibility type of cancer and incidence of cancer disease between males and females.

Table 1. Susceptibility type of cancer and incidence of cancer disease between males and females.

Types of cancers	**Mean ± SE**
Non hodgkin lymphoma	Male
Female	1.5±0.541 *
Hodgkin lymphoma	Male
Female	3±0.421 *
ALL	Male
Female	1±0.321
RMS	Male
Female	2.53±0.325 *
Neuroblastoma	Male
Female	2±0.412 *
Osteosarcoma	Male
Female	2.512±0.1254 *

Results was expressed as mean ± standard error (SE).

(*) significant difference ($p \leq 0.05$)

The most common type was ALL ~60%, while neuroblastoma came secondly, Hodgkin's lymphoma, R. M. S and osteosarcoma come next with slightly differences, while non-Hodgkin's lymphoma was the least common with a significant difference of (3.25+-0.125) comparing to ALL as showed in table (2-2).

Table 2. Common types of cancer in males and females.

Types of cancers	Non-hodgkin lymphoma Mean ±SE	Hodgkin lymphoma Mean ±SE	ALL Mean ±SE	RMS Mean ±SE	Neuroblastoma Mean ±SE	Osteo-sarcoma Mean ±SE
Non hodgkin lymphoma		0.75±0.354	3.25±0.125 *	0.5±0.148	1.5±0.654 *	0.25±0.124
Hodgkin lymphoma	0.75±0.321		2.5±0.3211 *	0.25±0.236	1.16±1.22	0.5±0.365
ALL	3.25±0.125 *	2.5±0.3211 *		2.75±0.122 *	1±0.565	1.75±0.4521 *
RMS	0.5±0.148	0.25±0.236	2.75±0.122 *		1.75±0.4123 *	1.576±0.324
Neuroblastoma	1.5±0.654 *	1.16±1.22	1±0.565	1.75±0.4123 *		1.85±0.751 *
Osteo-sarcoma	0.25±0.124	0.5±0.365	1.75±0.4521 *	1.576±0.324	1.85±0.751 *	

Results expressed as mean ± standard error (SE).

(*) significant difference ($p \leq 0.05$)

The effect of commonly used chemotherapy was studied in this study and examined on number of different markers such as WBC, Hemoglobin, Platelets, Urea, and creatinine as explained in the following tables and figures which showed these findings.

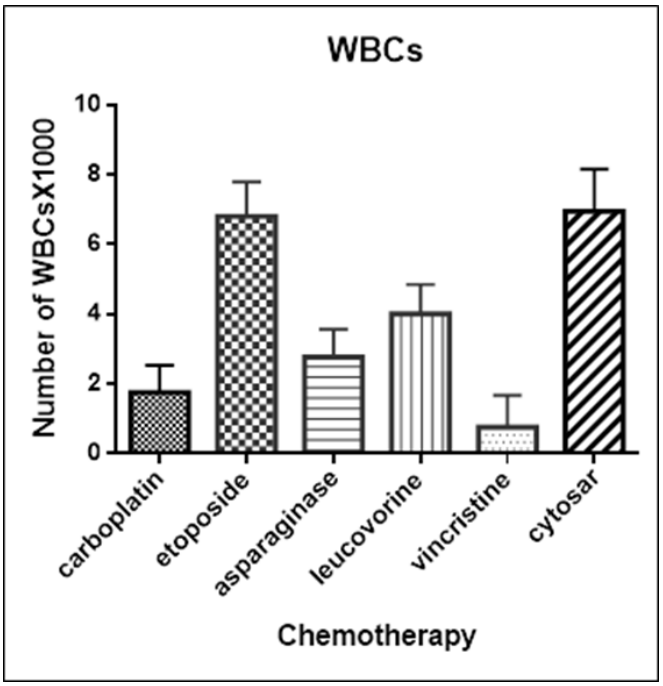

Figure 3. Effect of chemotherapy on number of white blood cells.

Table 3: Interaction between chemotherapy on number of white blood cells.

Chemoth-erapy	Carboplatin Mean ±SE	Etoposide Mean ±SE	Asparaginase Mean ±SE	Leucovorine Mean ±SE	Vincristine Mean ±SE	Cytosar Mean ±SE
Carboplatin		5.05±0.9339 *	1.015±0.565	2.25±0.600 *	1±0.6500	5.2±0.8500 *
Etoposide	5.05±0.9339 *		4.035±0.939 *	2.8±0.700 *	6.05±0.655	0.15±0.8500
Asparaginase	1.015±0.565	4.035±0.939 *		1.235±0.623	2.152±0.547	4.185±0.8500 *
Leucovorine	2.25±0.600 *	2.8±0.700 *	1.235±0.623		3.25±0.6500 *	2.95±0.600 *
Vincristine	1±0.6500	6.05±0.655	2.152±0.547	3.25±0.6500 *		6.2±0.9339 *
Cytosar	5.2±0.8500 *	0.15±0.8500	4.185±0.8500 *	2.95±0.600 *	6.2±0.9339 *	

Results expressed as mean ±standard error (SE).

(*) significant difference ($p \leq 0.05$)

Figure (3-5) showed the interaction between the drugs and Hb level, Leucovorine has the greatest potential for inducing anemia with a rate >10 while carboplatin has the lowest effect (3.27-+2.750)comparing to Leucovorine as showed statistically below in table (3-4)..

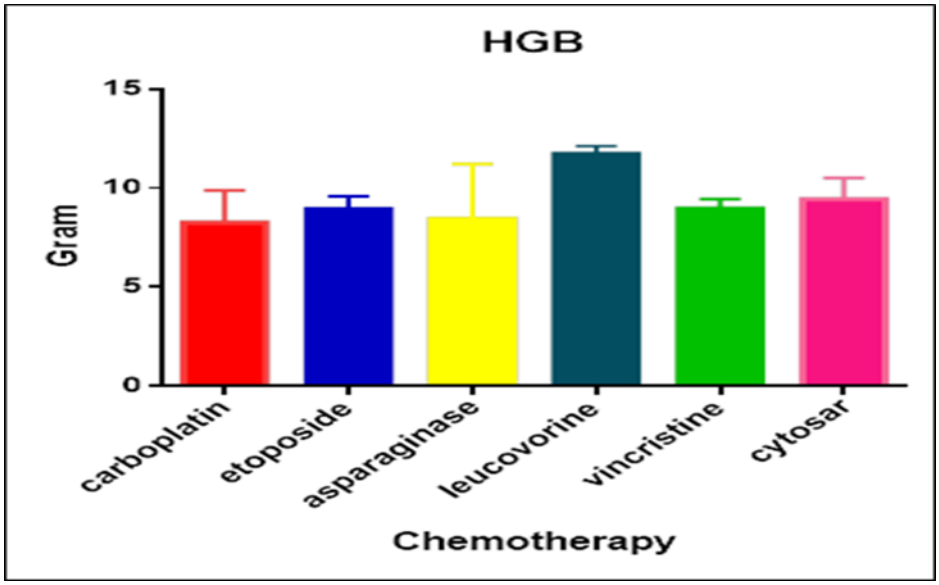

Figure 4: Effect of chemotherapy on Hemoglobin

Table 4: Interaction between chemotherapy on Hemoglobin

Chemotherapy	Carboplatin Mean ±SE	Etoposide Mean ±SE	Asparaginase Mean ±SE	Leucovorine mean±SE	Vincristine Mean ±SE	Cytosar Mean ±SE
Carboplatin		0.7±1.15	0.2±0.4500	3.44±1.950	0.72±0.350	1.2±0.7500
Eoposide	0.7±1.15		0.5±1.950	2.77±2.750	4.8±0.350	0.5±0.7500
Asparaginase	0.2±0.4500	0.5±1.950		3.27±2.750	0.5±0.3500	1±0.7500
Leucovorine	3.27±2.750	0.5±0.350	1±0.7500		2.77±0.350	2.275±0.850
Vincristine	0.72±0.350	4.8±0.350	0.5±0.3500	2.77±0.3500		0.5±0.6500
Cytosar	1.2±0.7500	0.5±0.750	1±0.7500	2.275±0.850	0.5±0.6500	

Results expressed as mean ±standard error (SE)

(*) significant difference ($p \leq 0.05$)

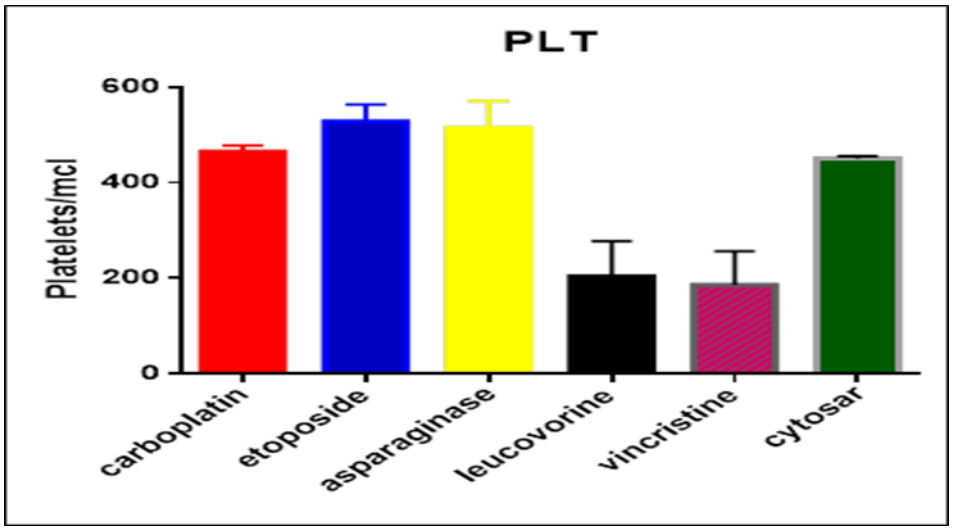

Figure 5. Effect of chemotherapy on platelet count.

Table 5. Interaction between chemotherapy on platelet count.

Chemoth-erapy	Carboplatin Mean ±SE	Etoposide Mean ±SE	Asparaginase Mean ±SE	Leucovorine Mean ± SE	Vincristine Mean ±SE	Cytosar Mean ±SE
Carboplatin		63±40	49±40	261±52 *	279±50 *	14.5±3.5
Etoposide	63±40		14±25	324±52 *	342±50 *	77.5±3.5
Asparaginase	49±40	14±25		310±52 *	328±50 *	63.5±3.5
Leucovorine	261±52 *	324±52 *	310±52 *		18±50	246.3±52.5
Vincristine	279±50	342±50	328±50	18±50		264.3±3.5
Cytosar	14.5±3.5	77.5±3.5	63.5±3.5	246.3±52.5 *	264.3±3.5 *	

Results expressed as mean ±standard error (SE).

(*) significant difference ($p \leq 0.05$)

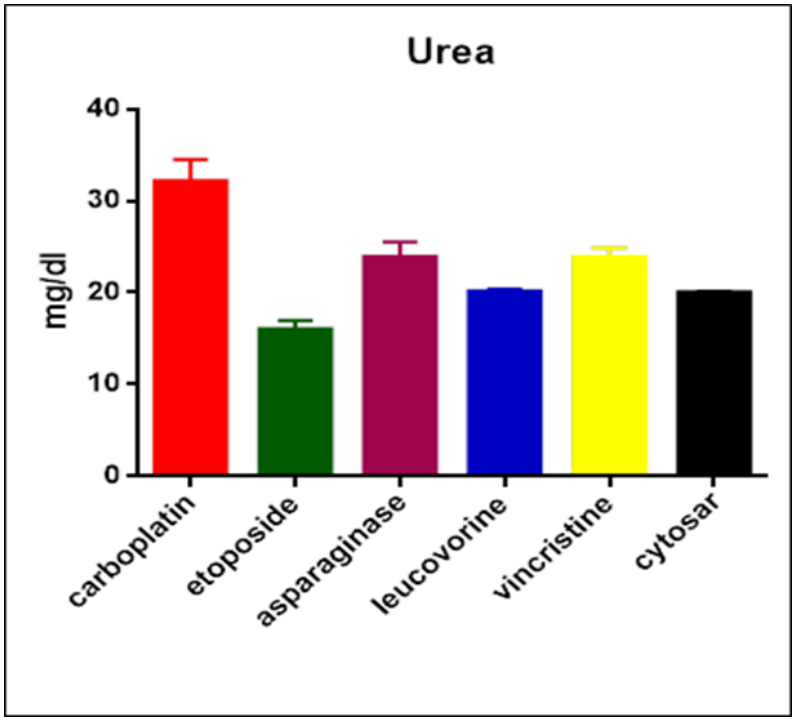

Figure 6: Effect of chemotherapy on urea concentration in plasma.

Table 6. Interaction between chemotherapy on urea concentration in plasma.

Chemoth-erapy	Carboplatin Mean ±SE	Etoposide Mean ±SE	Asparaginase Mean ±SE	Leucovorine Mean ±SE	Vincristine Mean ±SE	Cytosar Mean ±SE
Carboplatin		16.9±0.715 *	8.25±1.19 *	12.03±0.23 *	8.33±0.765 *	12.41±0.12 *
Etoposide	16.9±0.715 *		7.905±1.19 *	4.165±0.23	7.86±0.765 *	4.026±0.12 *
Asparaginase	8.25±1.19 *	7.905±1.19 *		3.74±0.23	0.042±0.765	3.85±0.12
Leucovorine	12.03±0.23 *	4.165±0.23	3.74±0.23		3.654±0.765	0.11±0.12
Vincristine	8.33±0.765 *	7.86±0.765 *	0.042±0.765	3.654±0.765		3.854±0.12
Cytosar	12.41±0.12 *	4.026±0.12 *	3.85±0.12	0.11±0.12	3.854±0.12	

Result expressed as mean ±standard error (SE).

(*) significant differences ($p \leq 0.05$)

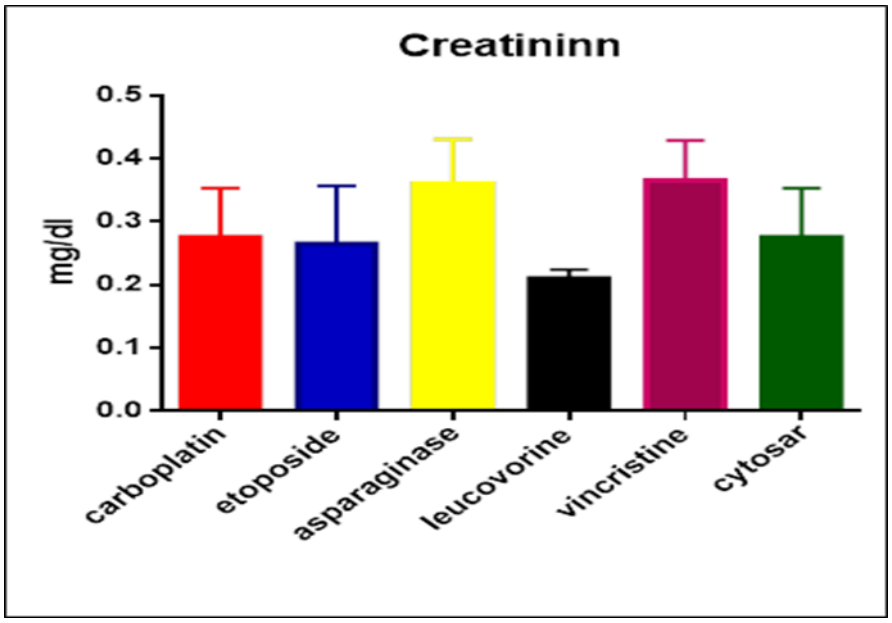

Figure 7. Effect of chemotherapy on creatinine concentration in plasma.

Table 7: Interaction between chemotherapy on creatinine concentration in plasma.

Chemotherapy	Carboplatin mean±SE	Etoposide mean±SE	Asparaginase mean±SE	Leucovorine mean±SE	Vincristine mean±SE	Cytosar mean±SE
Carboplatin		0.265±0.065	0.36±0.05	0.21±0.01	0.365±0.045	0.275±0.055
Etoposide	0.265±0.065		0.265±0.05	0.265±0.01	0.265±0.04	0.265±0.055
Asparaginase	0.36±0.05	0.265±0.05		0.36±0.01	0.36±0.04	0.36±0.055
Leucovorine	0.21±0.01	0.265±0.01	0.36±0.01		0.21±0.04	0.14±0.055

Results expressed as mean ±standard error (SE).

(*) Significant difference ($p \leq 0.05$)

Discussion

Patient's treatment from cancer with chemotherapy is associated with considerable toxicity this study was performed to evaluate most common side effects related to different chemotherapy drugs and the significant interactions between these agents when given together. Cancer incidence rate were lower in rural areas (41.53%) than in urban areas (56.45%) as showed in figure (1), in general cancer risk is higher in urban areas although the incidences differ among different types of cancer (39).

Figure (2) and table (1) showed the differences between males and females in the most common type of cancer incidence since, Hodgkins and non-Hodgkin's lymphoma are more common in males. While neuroblastoma, osteosarcoma and RMS are more common in females. During childhood, as mentioned above, few cancers are more common in females, but overall, males have higher susceptibility and this could be due to hormonal or behavioral differences besides immune surveillance, genome surveillance mechanisms also differ in efficiency (40).

ALL was occupy about ~60%, neuroblastoma was the second, Hodgkin's lymphoma, RMS and osteosarcoma come next with slightly differences, while non-Hodgkin's lymphoma was the least common with a significant difference of (3.25±0.125) comparing to ALL as showed in table (2). Chemotherapy effects on different biological markers were studied in this study such as white blood cells, hemoglobin concentration, and platelets in addition to the urea and creatinine concentration. This is important to explain the effect of chemotherapy in attempt to reduce their side effects and toxicities on children patients.

Cytosar and etoposide have the greatest effects on WBC counting as in figure (2) and have significant interactions with other chemotherapeutic agents as explained in table (3). Vincristine has the lowest effect on WBC counting~2000 with a significant difference of

(6.2+-0.9339) comparing to cytosar, Leucovorine , asparaginase and carboplatin has moderate effects with a slight difference between them, as showed statistically in table (3)and figure (3). While it could cause increasing in the number of white blood cells when give for long course(13). These interactions should be of greater concern when prescribing to the patient to minimize and prevent their toxicities.

In the same way, testing chemotherapeutic effect on hemoglobin concentration were carried out and the results are explained in figure (4) and table (4). All tested agents showed approximately similar effects in inducing anemia(14). While no significant interaction between them effect hemoglobin.

Etoposide and asparaginase have the greatest effect on platlets count >500 and the potential to cause thrombocytopenia by a slight difference of (14±25), while vincristine has the lowest effect by ~200 and a significant interaction of (342±50) comparing to etoposide as showed in table (5) and fig. (5). There are considerable number of interactions between chemotherapeutic agents explained in table 5.these interactions showed be reduced and minimized when prescribing such drugs. As other studied which explain the effect of chemotherapy on platelets account(15)

Serum urea level was effected largely by carboplatin nearly more than 30 while etoposide has the lowest effect comparing to carboplatin with a significant difference of (16.9±0.715) as showed statistically in table (6), fig (6). This result agree with other researches which examined such effects.

Vincristine and asparaginase have the greatest effect on creatinine level more than 0.3 and the rest of drugs showed a close values as showed statistically in table (7), fig (7) (16).

In spite of the advantages of chemotherapeutic agents, they are not without adverse and sometimes harmful effects. Therefore, it is important to follow up patients taken chemotherapeutic agents in order to observe and deal with any unwanted effects during course therapy.

Conclusion:

This study has revealed a certain toxicity of chemotherapeutic drugs and their side effects in order to be familiar with them and their mechanisms to choose the right treatment protocol and to minimize their side effect working to enhance their effectiveness and efficiency to minimize mortality due to the high toxicity. Besides putting the right protocols, this is important to make sure that poor people and low socioeconomic patients could reach to proper health care and good nourishment.

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