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RESEARCH ARTICLE

STUDY OF THE EFFECT OF CHEMOTHERAPY IN BONE UPTAKE TO ^{99M}TC-MDP AND THE GFR AMONG BREAST CANCER PATIENTS

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ABSTRACT

The bone scan is the accepted initial imaging modality for skeletal metastases. Some patients use chemotherapy in the initial stages before and after surgery for breast cancer patients according to the international protocol; this study aimed to evaluate the time elapsed between the bone scan and chemotherapy dose that effected on renal function using GFR measurement. It is a retrospective study designed and conducted in the Nuclear Medicine Department, King Abdulla medical city (KSA) which included 150 female breast cancer patients with age ranged between 25-75 years, and their weight ranged 40-120 kg. All patients were diagnosed with breast cancer according to the histopathology report and were received chemotherapy treatment except group control. The results of this study revealed that the most common drugs used for adjuvant and nan adjuvant is (cisplatin combination) chemotherapy, the effects of this types of drugs on GFR is with significant correlation of - 0.07 when the GFR after chemotherapy treatment id measured compare to the GFR values of the same patients before the chemotherapy treatment was given , also the result revealed that all counts from the bone target in the bone scan was decreased after treatment in all groups and there are a direct linear relationship between the acquired counts and the elapse time after chemotherapy, the coefficient of this relationship indicates that the researcher applied the specific threshold segmentation in order to increase the image quality by decreasing the values of the counts per background pixel and increased the value of counts per bone region pixel and increasing the ratio between the background counts to the bone region counts per pixel, the result showed a strong significant correlation of 0.733 between the applied threshold significant and the ratio of bone counts to the background counts, the researcher set a values of recommended threshold segmentation which should be applied for bone scan image to the patients treated with chemotherapy, these set of segmentation values depended on the time intervals between the bone scan and the chemotherapy treatments in order to increase the image quality to be quite diagnosable, the threshold segmentation should be increased by a factors of 54.4%, 130%, 218.2% and 278.2% form the threshold segmentation of the normal control groups of patients for bone scan after 4,3,2 and 1 weeks from chemotherapy treatments respectively, this study concluded that the suitable time for bone scan posts chemotherapy is four weeks unless a care of image processing are taken into consideration in term of threshold values in order to increase the bone target counts Vs. the background non target counts.

INTRODUCTION

Bone is the most common site to which breast cancer metastasizes. Between 30% and 85% of patients with metastatic breast cancer will develop bone metastases during the disease [(2)]. Bone also represents the first site of metastasis for 26% to 50% of patients with metastatic breast cancer. Complications of bone metastasis include bone pain, pathologic fractures (the incidence of which ranges from 16% to 60%), hypocalcemia, and spinal cord compression, any of which can profoundly impair quality of life. [(3)] Technetium-99m methylenediphosphonate (Tc-99mMDP) is one of the

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preferred bone-seeking agents used for the diagnosis of various malignant and benign bone diseases. It is preferentially adsorbed in immature amorphous calcium phosphate and mature hydroxyapatite crystal [4]. Breast cancer is an abnormal cell growth, the growth of which is uncoordinated with the normal one and persists with excessive manner after the cessation of the stimuli that evoke it, with a tendency to metastasize to other vital organs via the circulatory system, lymphatic system, and direct invasion [6].

The phenomena of cancer metastasize due to some properties of the cancer cell, as cancer cells show uncontrolled mitotic divisions causing unorganized growth, amebic movement, and cancer cellsdo not undergo differentiation. The breast cancer is commonly affecting female with a percentage rate equal to 34.5% in Sudan [7], and scarcely among males 0.1%. Such high incidence of breast cancer among female also confirmed by Kathleen et al., [8] in which they ascribed the high incidence of female breast cancer to estrogen hormone that promotes the development of breast cancer. Chemotherapy Treatment uses medicine to weaken and destroy cancer cells in the body, including cells at the original cancer site and any cancer cells that may have spread to another part of the body. Chemotherapy, often shortened to just "chemo," is a systemic therapy, which means it affects the whole body by going through the bloodstream. Chemotherapy was used to treat the early stage, invasive breast to get rid of any cancer cells that may be left behind after surgery and to reduce the risk of the recurrence, advanced stage cancer to destroy or damage the cancer cells as much as possible and in some cases, chemotherapy is given before surgery to shrink the tumor size. [9].

MATERIALS AND METHODS

Study design

It is a retrospective study designed and conducted in the Nuclear Medicine Department, King Abdulla medical city (KSA) which included 150 female breast cancer patients with age ranged between 25-75 years, and their weight ranged 40-120 kg. All patients were diagnosed with breast cancer according to the histopathology report and were received chemotherapy treatment except group control ,they referred to the department of nuclear medicine in king Abdulla medical city, for bone scan study examination , they have no other diseases such as diabetes, hypertension and kidney disease , with normal GFR. Total sample were 410 patients 260 patient were excluded due to some reasons such as (disease, age, previous history, test before don't do requested). 150 female confirm diagnoses single breast cancer in the first stage were distributed into five groups, namely, control group (G1) and chemotherapy (cisplatin combination) groups (G2, G3, G4, G5). The different between the Groups (from G2 to G5) is the time elapsed between the chemotherapy administration and the bone scan which is 4, 3, 2 and 1 weeks respectively. Pre-therapy and after GFR bone Scintigraphy was obtained for all the groups. Cisplatin combination chemotherapy was given as infusion by the same type of Chemotherapy Company and calculated the dose independent on patient weight and other clinical criteria. Post-therapy bone scintigraphies were obtained after seven days from one cycle (G2), 14 days from one cycle (G3), 21 days from one cycle (G4) and 28 days from one cycle (G5), respectively. All groups bone Scintigraphy was obtained GFR base line they were also measured after chemotherapy and before bone scan at the same time within two days of bone scan also the dose of the radiopharmaceutical (99mTc-MDP) is giving by the weight factor.

Study protocols methods (techniques)

Bone scan was done using SPECT gamma camera GE general electric - made in USA 2014. SPECT gamma camera protocol: All the cases were examined in the supine position with the standard position of bone scan using the following sequences. Spots views and whole body sped stander (10m/m) pixel 1024*256.System software included all data inter such as age Weight height control the data that helps in scanning.

Preparation of 99mTc-MDP injection

The MDP kits contain the sterile component in the lyophilized form which after reconstitution with pertechnetate solution a complex of methylenediphosphate (MDP) with technetium 99mTCformed, which show an affinity to hydroxyapatite of the bone tissue. Under sterile condition 5ml of sodium pertechnetate solution with maximum activity of 100-500mCi was added to the MDP vial content through the stopper. The vial Content was mixed for 20 minute. The pH value of the prepared Radiopharmaceutical has 5-7. The 99mTc-MDP preparation is administered within 6 hours of the preparation time (shelf life).

Patient preparations

All Patient was instructed to be well hydrated by drinking about 2 liters before and 2 of water during (between injection and scan) the patient must drink at least 2 liters of fluid between injection and image that is done for all patient . The patient was encouraged to avoid immediately before imaging if the catheter is present the back should be emptied before imagine (this excluded in this sample)

RESULTS

The following results highlighting the bone scan in Saudi Arabia during the period of 2015-2017, incidence% based on GFR, duration of chemotherapy before the bone scan, and variation incidence with the patient taking chemotherapy, the involved Includes period of chemotherapy before the bone scan and role of image enhancement. In this part tables and figures presented the results of the study

DISCUSSION

The bone scan is the accepted initial imaging modality for skeletal metastases. Some patients use chemotherapy in the initial stages before and after surgery for breast cancer patients according to the international protocol; this study aimed to evaluate the time elapsed between the bone scan and chemotherapy dose that effected on renal function using GFR measurement. It is a retrospective study designed and conducted in the Nuclear Medicine Department, King Abdulla medical city (KSA) which included 150 female breast cancer patients with age ranged between 25-75 years, and their weight

Table 1. That shows statistics of group G1

		age	weight	height	A	B	C	D	E	F	G	H	I	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		51.17	70.20	157.00	2313103.13	13.43	4.77	20.43	4.57	250.23	.98	97.07	97.07	28.60
Std. Deviation		13.626	15.410	10.017	678077.430	1.960	1.104	4.508	1.406	1.104	.004	10.983	10.352	6.770

Values of counts in row data image (A), the threshold applied (B), background per pixel (C),value of the bone target per pixel (D), ratio of the bone to the backgrounds pixels (E),NewImMax bone highest value(f), ratio of highest bone value(255) (G) ,values of GFR after the chemotherapy (H), base line GFR (I)

Table 2. That shows statistics of group G2

		age	weight	height	A	B	C	D	E	F	G	H	I	BMI
N	Valid	Valid	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	Missing	0	0	0	0	0	0	0	0	0	0	0	0
Mean			47.27	157.13	66.23	2096640.07	20.73	7.27	3.40	24.57	.97	247.73	100.87	99.33	27.00
Std. Deviation			14.501	10.105	9.964	566139.670	2.434	.828	.724	4.199	.003	.828	11.599	11.751	4.871

Values of counts in row data image (A), the threshold applied (B), background per pixel (C),value of the bone target per pixel (D), ratio of the bone to the backgrounds pixels (E),NewImMax bone highest value(f), ratio of highest bone value(255) (G), base line GFR (H), values of GFR after the chemotherapy (I)

Table 3. That shows statistics of group G3

		age	weight	height	A	B	C	D	E	F	G	H	I	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		51.10	155.53	67.50	1986369.13	30.90	9.10	27.77	3.07	245.90	.96	93.17	96.63	28.13
Std. Deviation		12.829	9.933	15.359	502988.836	3.517	.885	4.216	.828	.885	.003	10.406	10.005	7.811

Values of counts in row data image (A), the threshold applied (B), background per pixel (C),value of the bone target per pixel (D), ratio of the bone to the backgrounds pixels (E),NewImMax bone highest value(f), ratio of highest bone value(255) (G) ,values of GFR after the chemotherapy (H), base line GFR (I)

Table 4. That shows statistics of group G4

		age	weight	height	A	B	C	D	E	F	G	H	I	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		53.70	155.37	76.53	2120879.27	42.73	11.37	28.17	2.50	243.63	.96	89.13	95.07	31.67
Std. Deviation		11.931	8.536	16.571	741744.846	3.216	1.426	4.161	.630	1.426	.006	8.740	8.948	6.551

Table 5. Shows statistics of group G5

		age	weight	hight	A	B	C	D	E	F	G	H	I	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		56.87	155.03	76.00	2139659.53	50.77	14.87	30.13	2.17	240.13	.94	82.40	92.50	31.60
Std. Deviation		10.061	8.888	14.546	765321.516	2.501	2.403	3.213	.461	2.403	.009	7.811	7.904	5.575

ranged 40-120 kg. All patients were diagnosed with breast cancer according to the histopathology report and were received chemotherapy treatment except group control; this study focuses on oncology patients considered for chemotherapy. We evaluated the impact of different GFR methods on the reduction of cisplatin dose. The study population consisted of 150 consecutive oncology patients female confirm diagnoses single breast cancer in the first stage were distributed into five groups, namely, control group (G1) and chemotherapy (cisplatin combination) groups (G2, G3, G4, G5). Pre-therapy and after GFR bone scintigraphies were obtained in all the groups before and after chemotherapy treatment. Chemotherapy used for the treatment of many tumors. Some of these tumors have a high affinity to metastasize to bone, such as genitourinary system tumors, and neuroblastoma, Bone scintigraphy is a screening test to demonstrate bone metastases and is sometimes performed during or within a few days following chemotherapy studied the renal accumulation index of Tc-99m MDP following chemotherapy.

Treatment and demographic data are presented in Tables and figures for this study revealed that for control group (G1) patients their mean of age, weight, and height is 51.2 years, 70 Kg and 157 Cm respectively. The bone and background counts per pixel for this group mean of counts are 20.43 and 13.43 respectively with a ratio of 4.57 and 250.23 as maximum pixel counts and the mean of GFR is 97.07 with 28.60 mean BMI, a significant correlation was found between the base line GFR and ration of the bone highest value of -.074, and this significant correlation increased significantly when comparing the value of GFR after chemotherapy treatment to the values of maximum bone counts to be -.007. There is strong significant correlation between the highest bone values counts in the image of the bone scan and ration between the background to bone ratio which indicate strongly to the hypothesis that the chemotherapy somehow affects the absorption of bone-seeking agents in the bone which result in increased the background, increasing in background result in the poor imaging quality of the bone scan, the value of this strong significant correlations between the maximum bone absorption per pixel and the ratio between the bone to background values is .733. The strong significant correlation is also founded between the baseline GFR and GFR value after chemotherapy (0.975) which indicate the renal impairments in term of GFR affected by chemotherapy

Table (2) showed that the patient's bone scan after four weeks of chemotherapy treatment, the mean values of counts in row data image is 2096640.07 counts compare with the 2313103.13 counts for control group patients (Table 1), the threshold applied to this group of patients is 20.73 compare to the 13.43 to the control group in order to provide the same image resolution of the bone, the background per pixel means in this patients group is 7.27 which is more than the value of control group patients (4.77) while the mean value of the bone target per pixel is 24.57, and the mean ratio of the bone to the backgrounds pixels is 3.40, the mean values of base line GFR for this group of patients is 100.87 while the mean values after the chemotherapy is 99.33. Table (3) for the group of patients examined for bone scan after three weeks from receiving a chemotherapy treatment cycle with dysplatine, showed that the mean counts in row data image is 1986369.13 counts with 30.9 mean threshold segmentation applied to the image to be adequate interpreted image, the mean value of backgrounds per pixel is 9.10, and the bone pixel means value is 27.77 while the mean values of the ratio of the bone per pixel per background is 3.07, from the renal profile of this group of patients, the mean value of the baseline GFR is 96.63 while the mean values of GFR after the chemotherapy treatment is 93.17. Table (4) for the group of patients who scanned using 99mTc-MDP bone seeking agent after two weeks of chemotherapy received intravenously, the values showed 2120879.27counts as mean value of counts in the row data images of the all patients in this group before any type of processing, while the mean threshold segmentation value applied for processing the image is 42.73 with 43.50 median and 3.216 standard deviation, the value of background non-target per pixel is 11.37 mean, 12 median with 1.426 standard deviations, for this group of patients the mean, median and standard deviation of the counts from bone region per pixel is 28.17, 28, and 4.161 respectively, the ratio of bone region per pixel per backgrounds region per pixel is measured to be 2.50, 2 and 0.630 mean, median and standard deviation respectively, the GFR baseline for this group of patients is 95.07 mean with 8.948 standard deviations compared to 89.13 mean value and 8.740 standard deviations for the GFR values measured after the patients treated with a chemotherapy cycle.

Values of patients scanned after one week from chemotherapy line represented in table (5), the mean, median and standard deviation values of the counts in the row data images of the patients before any filter added or processing carried out is 2139659.53 counts, 1957884.50 counts, and 765321.516 counts respectively while the mean threshold segmentation values applied for image processing in order to increase the image resolution is 50.77 with 2.501 as standard deviation value, the mean values of background per pixel for this group of patients is 14.87 with 15 as median and 2.403 as standard deviation while the value of bone per pixels measured to be 30.13, 30 and 2.403 as mean, median and standard deviation respectively, the mean value of ratio between the bone and the background counts per pixel is 2.17 with 0.461 standard deviation, the mean value of base line GFR for this group of patients is 92.5 with 7.904 standard deviations compared to 82.4 mean value of the GFR after the patients treated with cycle of chemotherapy. From the current study result patients who scanned after four weeks from chemotherapy treatment the counts in the row data image before added filter of threshold segmentation was decreased (2096640.07) compared to the mean values of the same parameter of the control group patients (2313103.13), and this value is decreased in the patients scanned after three weeks from chemotherapy cycle treatments with mean values of 1986369.13while this value is also decreased for the other rest of groups i.e. patients scanned two and one weeks after chemotherapy treatment compare to the control group, but this value was found to be considered more than the mean value of the same parameters for the other groups which includes the patients scanned for bone scan after four weeks from treated with chemotherapy and those scanned after three weeks from received intravenously chemotherapy cycle which indicate that the overall counts in the row data image was decreased after chemotherapy compared to the patients without and history of cancer nor chemotherapy treatments but without defined factors for measuring the percentage of decreasing. The mean value of background/pixel

is showed to be increased as the time between chemotherapy treatments and bone scan imaging decreased, the value is 4.77 for normal control group patients, and these value increased to be 7.27 for patients scanned for bone using gamma camera SPECT system after four weeks of administration of chemotherapy as treatments essential for cancer, and then this value showed being 9.10 for group of patients who scanned for bone after three weeks from chemotherapy treatments, then increased up to the value of 11.37 for the patients scanned after two weeks from chemotherapy administration and the value be 14.87 for the patients group which were scanned after only one week from chemotherapy treatments line. Physiologically the unbound 99mTc must be execrated from the body via renal system, this free 99mTc which can came from hydrolyzed reduced technetium inventory or can be result from in vivo dissociation of the components after injected to the patients intravenously, so any impairments in the renal system lead to slower clearness of this Tc99m, when compared to the value of background per pixel to the GFR values the researcher find that there was strong significant correlation of 0.381between these parameters, this is so clear from the change that happened and showed in the GFR values after chemotherapy, when compare this values to the normal control group of patients the researcher found that there is a proportional relationship between the GFR value and the chemotherapy treatments, the mean value of normal patients is 97.07 while this value was decreased rapidly for patients received chemotherapy and then increased as the time interval between chemotherapy treatments and the GFR value measured increased, so that the impairments of the renal system from chemotherapy treatments was found and considered to be temporarily impairments with the value function of time, this hypothesis explained the increased the background per pixel values in all the patients group after chemotherapy when scanned by gamma camera to evaluate the bone, and also found to be function of time values as this values increased as the time between the chemotherapy treatments and bone scanned decreased, the GFR mean values were 99.33, 93.17, 89.13 and 82.40 for the patients treated with chemotherapy and GFR measured 4,3,2 and 1 weeks after chemotherapy treatments respectively.

Form the all above-mentioned tables the result showed that the values of the bone counts per pixel have a direct relationship with the time between the bone scan and chemotherapy treatments. The threshold segmentation applied in image processing to the image to result in a diagnosable resolution image has a proportional relationship to the time between bone scan and chemotherapy , which indicate that the little bone absorption of the 99mTc-MDP and low image resolution can be increased by changed the threshold segmentation applied to the image, when compared the mean value of threshold for all groups of patients treated with chemotherapy to the threshold segmentation for patient without history of chemotherapy (13.43), this value changed to be 20.73, 30.90, 42.73 and 50.77 for the 4,3,2, and 1 week between chemotherapy treatments and bone scan respectively, this value showed strong significant correlation of 0.693. when compared the value of ratio of mean background pixel counts to the mean bone region pixel counts the researcher found that there is direct relationship between the value measured and the time interval between the chemotherapy treatments and bone scan imaging, the mean value of this ratio to the normal patients whom dose not treated with chemotherapy is 0.98, and the ratio showed to be decreased after the patients having chemotherapy to be 0.94, 0.96, 0.96 and 0.97 for patients scanned for bone after one, two, three and four weeks from chemotherapy treatments respectively. When the researcher applied the specific threshold segmentation in order to increase the image quality by decreasing the values of the counts per background pixel and increased the value of counts per bone region pixel and increasing the ratio between the background counts to the bone region counts per pixel, the result showed a strong significant correlation of 0.733 between the applied threshold significant and the ratio of bone counts to the background counts the researcher set a values of recommended threshold segmentation which should be applied for bone scan image to the patients treated with chemotherapy, these set of segmentation values depended on the time intervals between the bone scan and the chemotherapy treatments in order to increase the image quality to be quite diagnosable, the threshold segmentation should be increased by a factors of 54.4%, 130%, 218.2% and 278.2% form the threshold segmentation of the normal control groups of patients for bone scan after 4,3,2 and 1 weeks from chemotherapy treatments respectively.

Study done by Daugaard G et al (12) observed a high renal uptake of Tc-99m MDP within 28 days after chemotherapy also high renal accumulation following chemotherapyobserved by]. Ozhan et al (13) .The present study results differed with this research relative to their application to non- human rabbits. This difference is different to the difference of the biological factor between humans and animals, as well as the method of measuring the effect of blood, the difference in measurement and the time period of measurement and cannot be considered a study identical to this research due to the difference of all factors, Most of the results of this research have been agreed with results of the study done by Gihad (14) found observation of this study the counts rate reach the acceptable level after 28 days,] Murphy et al (15) also observed in this study as it markedly decreases sensitivity for bone disease. Bone Scintigraphy should be timed so that it is performed before etidronate treatment or cisplatin, if that is not possible, more than 2 to 4 weeks after the therapy has been completed.

Conclusion

It was observed that there was significant reducing in the reading of the counts at adjusted levels according to the period before and after the chemotherapy. This effect increases as the period between bone scan study and chemotherapy decreases.

- Tc-99m MDP bone Scintigraphy, can be performed imaging technique for detecting bone metastases, can be performed at a period of four weeks after chemotherapy.
- The study findings revealed that the duration of effect of Chemotherapy on bone Scintigraphy
- Oncology patients are a very special group of patients who differ from general population; there are significant individual differences between GFR before and after chemotherapy

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