J. of Obst. & Gyn. of India Vol. 52, No. 4 : July/August 2002 Pg 70-72

"Effects of 5-Fluorouracil on Serum Lipids, Lipoproteins and Apolipoproteins (A-1 & B) in Postmenopausal Women With Breast Carcinoma"

Deepa Sharma, Poulamy Mandal, Meenakshi Bishnol, Usha Sharma, V. S. Singh

Department of Biochemistry and Department of Obstetrics & Gynaecology, I.L.R.M. Medical College, Meerut.

Summary

The effect of cytotoxic chemotherapeutic drug, 5-fluorouracil on serum lipids, lipoproteins and apolipoproteins was studied in 27 postmenopausal breast cancer patients. Out of these 9 were suffering from vascular complications (5 from cardiovascular & 4 from cerebrovascular disease). A short term evaluation of serum lipids, lipoproteins and apolipoproteins was made before (i.e. at baseline) and 1 and 2 months after 5-FU administration. All the patients were given 600 mg/m2/day 5-FU by i.v. for 10-15 days. A significant reduction is serum TC was observed 1 & 2 months after the administration and significant elevations in serum HDLC and Apo A-1 were observed 2 months after 5-FU administration in postmenopausal patients of breast carcinoma (both with and without vascular complications), when compared with corresponding baseline values. However, reduction in TG level was not statistically significant. Serum Apo-B level & Apo A-1/Apo B ratio showed atherogenic elevations, when compared with corresponding baseline values but the elevations were statistically insignificant.

From the results of the present study, it was revealed that the administration of 5-fluorouracil might interfere lipids, lipoproteins and apolipoprotein metabolism and induce antiatherogenic effects on existing vascular complications (both cerebro – and cardiovascular) by improving serum of TC, HDLC and Apo-A-I levels in postmenopausal patients of breast cancer.

Introduction

The cytotoxic chemotherapeutic drug, 5-fluorouracil, has been used for the treatment of breast cancer, gastrointestinal tumours, head-neck and other solid tumors. (Rooney et al., 1985; Ansfeild et at., 1997 and Henderson et al., 1990). The primary toxic effects of 5-flurorouracil are on the gastrointestinal mucosa and bone marrow. 5-Fluorouracil is administered alone or usually in combination with other drugs (such as cyclophosphamide and methotrexate) as an adjuvant chemotherapy. The possible mechanism for cytotoxicity caused by 5-fluorouracil, may be the inhibition of DNA synthesis induced by fluorouridine triphosphate and fluorodeoxy uridine monophosphate the metabolic products of 5-fluorouracil (Klubes et al., 1978). The onset of menopause is usually accompanied by well established changes in serum lipids, lipoproteins and apolipoproteins, an atherogenic effect attributed to estrogen deficiency, (Newnham, 1993 and Stevenson et al, 1993) and contributes to the development of vascular complications.

The recent data regarding the effect of 5-fluorouracil on lipoproteins and apolipoproteins metabolism are sparse due to uncommon use of 5-fluorouracil in postmenopausal breast cancer patients. The present study was undertaken to assess the effects of 5-fluorouracil on serum lipids, lipoproteins and apolipoproteins (A-1 & B) in postmenopausal patients of breast carcinoma.

Abbreviations used :

5-FU	–	5- Fluorouracil
TC	=	Total Cholesterol
TG		Triglyceride
HDLc	–	High density lipoprotein cholesterol
APO – A 1	=	Apolipoprotein A-1
APO-B	–	Apolipoprotein B
HL	=	Hepatic lipase

Subjects & Methods

Patients : The present study was carried but on histologically confirmed, 27 postmenopausal patients of breast carcinoma, attending the department of Gynaecology & obstetrics, SVBP Hospital, LLRM Medical College, Meerut. All the subjects had undergone spontaneous menopause and were aged between 50-60 years and were at primary and secondary stages of breast carcinoma. None had received endocrine treatment or adjuvant chemotherapy atleast for last 6 – 12 months. Out of 27 patients, 9 were suffering from vascular disease (4 from cerebrovascular and 5 from cardiovascular). The clinical and family history of all the subjects were recorded and those having previous history of nephrotic syndrome, hepatic disease, thyroid dysfunction or diabetes mellitus, which might fluctuate serum lipids, were excluded from the present study.

Dose of 5-FU : All the patients of breast cancer were given 600 mg/m2/d 4-FU i.v. as a single chemotherapy for 10-15 days.

Collection of blood samples : The blood samples of all the subjects were withdrawn by venipuncture, after an overnight fast (12 hours), before the initiation of therapy (i.e. baseline) and 1 and 2 months after 5-FU administration. The serum was separated by centrifugation for the estimation of TC, TG, HDLc, Apo A-1 and Apo-B.

Laboratory Analysis : Serum TC and HDLc were estimated by enzymatic CHOD-PAP method (Merck Commercial Kits, Cat No. 14366 for TC and Cat No. 14210 alongwith Cat No. 14366 for HDLc). TG by enzymatic GPO-PAP method (Merck Commercial Kit, Cat No. 14354) Apo A-1 and Apo-B by immunochemical assay (Orion Diagnostica kits, FINLAND Cat No. 67265 & 67249).

Observations

5-FU induced changes in serum lipoproteins and apolipoproteins (A-1 & B) levels in postmenopausal breast cancer women are given in Table I

Results and Discussion

In the present study, serum total cholesterol level of postmenopausal breast cancer patients (n 27) was found to be decreased significantly 1 and 2 months after 5-FU administration as compared to that of baseline value ($p<0.05$: 0-1 months and $p<0.01$ 2 months) whereas serum HDLc ($p<0.05$. 0-2 months) and Apo A-1 (<0.05. 0-2 months) were found to be elevated significantly 2 months after the therapy as compared to corresponding baseline values.

The plasma DHL concentration is regulated by multiple mechanisms such as synthesis of Apo A-1 and A-II in the liver, lipoprotein lipase, hepatic lipase, cholesteryl ester transfer protein and LCAT activities. The increase in serum HDLc level could be partly related

Table I
5 – Fluorouracil Induced Changes in Serum Lipids, Lipoproteins and Apolipoproteins (A-1 & B) in postmenopausal patients of breast cancer

Parameters (mg/dl)	Postmenopausal patients of breast cancer receiving 5-Fluorouracil (n-27)		
	Baseline	After 1 months of 5-FU administration	After 2 months of 5-FU administration
	mean±S.D.	mean ± S.D.	mean ± S.D.
TC	228.58 ± 15.9	222.1 ± 7.69*	212.61 + 10.62**
TG	209.36 ± 26.1	199.7 ± 17.2^{NS}	195.3 + 15.6^{NS}
HDLC	38.09 ± 6.1	39.75 ± 6.1 ^{NS}	47.3 ± 7.97*
Apo A-I	131.25 ± 4.7	136.73 ± 8.72^{NS}	140.1 ± 13.93*
Apo – B	138.29 ± 19.73	142.86 ± 12.98^{NS}	147.06 ± 10.4 ^{NS}
Apo A-I / Apo – B	0.95 ± 0.39	0.96 ± 0.43^{NS}	0.95 ± 0.42^{NS}

^{NS} – Non Signifiant
* = $p<0.05$
** – $p, 0.01$

as compared to corresponding baseline values.

to a suppressive effect of estrogens on hepatic lipase (HL) activity (Newnham, 1993 and Seed crook , 1994). Consequently, estrogen deficiency in postmenopausal women is usually associated with lowering of HDLC and Apo A-I (Newnham, 1993 and Stevenson et al., 1993). Therefore, the elevation in serum HDLc and Apo A-I postmenopausal subjects after 5-FU administration is unexcepted and contradictory. The increase in HDL level in postmenopausal subjects is possible only if progesterone level also declines as progesterone has an action opposite to that of estrogen on hepatic lipase activity. Thus, the lack of progesterone may be able to overcome the action of estrogen deficiency on HL activity. Although in the present study levels of estrogen and progesterone were not measured but in some previous studies, chemotherapy castrations have been found to reduce estrogen and progesterone levels in postmenopausal breast cancer patients (Koyama et al., 1977 and Padamanabhan et al., 1987). Thus, the possibility that 5 FU might induce certain inhibitory effect on progesterone level or on HL activity, can not be denied. Unfortunately no data about the direct action of 5-FU on regulatory factors of HDL are available.

The effect of 5-FU on serum TC was more pronounced as compared to TG & HDLc. This might be either due to reduction in intestinal absorption or less biosynthesis in liver or increase in cholesterol clearance but the precise mechanism of action of 5-FU is still obscure. Similar results regarding the beneficial effect of 5-FU on serum TC level were obtained by Stathopoulos et al., (1995).

In the present study, serum Apo-B and Apo-A – I/ Apo- B ratio were found to be elevated, although insignificantly, after the administration of 5-FU, an atherogenic effect which may contribute to the development of vascular complications. Also in our previous study, elevated serum Apo-B level was recognized as potent risk factor for the development of vascular complications (Sharma et al., 1999). This rise in Apo-B might be attributed to declining or inhibitory effect of 5-FU on estrogens and progesterone, as these hormones increase the catabolism of Apo-B resulting in net reduction in circulating Apo-B. This hypothesis is also favoured by few previous studies (Koyama et al., 1977 and Padmanabhan et al., 1987). But the increase in HDLc and Apo A-I after 5-FU administration may partly negate the adverse effect of Apo-B level with respect to vascular complications (Bass et al., 1993). Similar results were obtained when serum lipids, lipoproteins, and apolipoproteins levels of patients of breast cancer suffering vascular complications, were analysed and compared with corresponding baseline values (separate data is not given here).

One possibility accounting for 5-FU induced serum lipoproteins and apolipoproteins concentration changes might be the toxic effects of 5 FU which may cause mucositis and disruption of bowel mucosa resulting in decreased food intake, an intestinal effect induced by 5-FU that can not be ignored. But in the present study, no such noticeable change in food intake of the patients was observed.

It is concluded from the results of the present study that 5-FU, besides its cytotoxic effect, induces some beneficial and antiatherogenic changes in serum. TC HDLc and apo A-I, thereby, minimizing the risk of vascular complications in postmenopausal breast cancer women and this drug is also found to be effective on existing vascular disease.

No doubt, more work is needed to be explored to assess the effects of 5 FU or other chemotherapeutic drugs on serum lipids, lipoprotein and apolipoprotein metabolism as the effects of chemical castration on plasma lipids, lipoproteins and aplipoproteins have not been extensively studied in post menopausal patients with breast cancer.

References

1. Ansfeild F; Klotz J; Nealon T; Hayes DS: Cancer, 39: 34, 1977
2. Bass KM; Newschaffer CJ; Klag MJ: Bush TI : Arch Intern. Med; 153: 2209, 1993.
3. Henderson KC; Garber JE; Breitmeyer JB; Hayes DF; Harris JR: Cancer; 66: 1439, 1990.
4. Klubes P; Conelly K; Cerna I; Mandel HG: Cancer Rev; 38 : 2325, 1978
5. Koyama H; Wada T; Nishizawa Y; Iwanaga I ; Aoki Y: Cancer; 39:1403, 1977.
6. Newnham HH: Bailliere Clin Endocrinol Metab ; 7 : 61, 1993.
7. Padmanabhan N; Wang DY; Moore JW; Rubens RD : Eur J Cancer Clin Oncol.: 23 : 745, 1987.
8. Rooney M; Kish J; Jacobs I; Cerna I : Cancer; 55: 1123, 1985.
9. Seed M; Crook D; Curr Opin Lipidol ; 5: 48, 1994.
10. Sharma D; Sharma U; Srivastava SSL, Singh VS: Indian Medical Gazette; 83(6): 208, 1999.
11. Stathopoulos GP; Stergiou SG; Perrea-Kostarelis DN; Dontas IA; Karamanos BG: Karayiannacos PE: Acta Oncologica; 34: 253, 1995.
12. Stevenson JC; Crook D; Godsland IF: Atherosclerosis; 98: 83, 1993.