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Methotrexate as an alternative to surgery in ectopic pregnancy: A new role for an old drug

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METHOTREXATE AS AN ALTERNATIVE TO SURGERY IN ECTOPIC PREGNANCY: A NEW ROLE FORAN OLD DRUG

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INTRODUCTION

Methotrexate has long been known as the agent of Choice for the treatment of gestational trophoblastic disease and is, therefore, well known to gynaecologists and oncologists. Because of its therapeutic effect in gestational trophoblastic disease, it appears well suited to eradicate trophoblastic tissue in aberrant locations. A number of reports in the past few years indicate that the drug could be effective in the management of unruptured ectopic pregnancies, thereby eliminating a surgical procedure which has been considered so far the only available treatment for such cases. The side effects of therapy with methotrexate are negligible. However, management with this antifolate requires very careful selection of the patients to avoid the possible risks of a rupture and consequent bleeding in the abdomen. Early detection of ectopic gestation facilitated by ultrasonography and sensitive assay systems for B-human chorionic gonadotrophin is necessary for success of the therapy. Resolution of ectopics is monitored by measuring plasma hCG levels during and after the treatment. Bypassing the risk, cost and morbidity of surgery and preservation of fertility appear to be the major benefits of this treatment. Ectopic pregnancy is a major problem in contemporary gynaecology. It occurs when the fertilized ovum embeds in some site other than the uterine decidua. Nearly all ectopic implantations occur in the fallopian tube but, to a very small extent, they can be in the ovary, cervix or the peritoneal cavity[1]. No statistical data are available about its incidence in Pakistan. However, according to the information by the Center for Disease Control in the United States, it appears to account for more than 1% of all reported pregnancies in America, indicating that a large segment of the fertile population in the western world is affected by this pathological condition[2,3]. Much higher incidence has been reported for countries where pelvic infections are more common, for example in the West Indies it is 1 in 28[1]. Since pelvic infections are quite common in third world countries, ectopic pregnancy could be contributing significantly to maternal mortality and infertility in Pakistan as well.

Traditional management

Salpingectomy which is often termed as a “radical approach” has been the traditional treatment for tubal gestation[4,5]. Strome for the first time described a conservative surgical approach to the treatment of ectopic pregnancy[6]. Development of microsurgical instrumentation has enabled a wide spread use of conservative techniques. The rationale behind conservative approach is the preservation of reproductive potential of the woman, although the repeat ectopic rates after radical and conservative management remain the same[7-9]. In the conservative treatment, the products of conception are carefully removed so that there is minimal damage to the tubal tissue. Depending upon the condition of the tube (ruptured or unruptured), location of gestation (interstitium, isthmus, ampulla) and the size of gestation, one of the following surgical techniques is selected and performed by laparoscopy or laparotomy, linear salpin-gostomy, segmental resection, salpingectomy[10]. Laparoscopic approach is usually not recommended when the maximum diameter of gestation is greater than 5 cm[10]. Post-operatively, an assessment of the functional activity of the residual trophoblastic tissue is made by serial measurements of serum fl-human chorionic gonadotrophin (B-hCG) [11]. There have been reports of persistent trophoblastic tissue following conservative surgical management which subsequently necessitated salpingectomy for these patients[12-15]. It was felt that perhaps a nonsurgical approach with an agent attacking the trophoblastic

tissue could have spared the fallopian tubes of these women. Since methotrexate (MTX) had been in use for the treatment of gestational trophoblastic disease for nearly 3 decades[16], it was considered to have a potential for pharmacological management of ectopic pregnancy.

MTX in the management of ectopic pregnancy

MDC therapy for resolution of ectopic pregnancy appeared attractive as this approach could spare patient's laparotomy and a tubal operation. Moreover, it was likely to result into less tissue trauma which is critical for preservation of reproductive function. Tanaka et al. and Miyazaki et al. were the first to report successful use of MIX in the management of interstitial and tubal pregnancies, respectively[17,18]. This approach resulted in an abrupt termination of the pregnancy and subsequent hysterosalpingography (HSG) revealed preservation of tubal patency. Development of sensitive radioimmunoassay for B-hCG levels in serum provided gynaecologists with a useful tool to monitor resolution of ectopic pregnancy following MIX therapy, because with the degeneration of trophoblastic tissue, there was rapid disappearance of serum f3-hCG associated with clinical well- being of the patient. During the past 8 years, there have been quite a few reports on systemic or local use of MIX in the treatment of unruptured tubal pregnancies[19-26]. An analysis of these reports indicates that in more than 200 tubal pregnancies treated with different MIX regimens, less than 5% of the patients required surgical intervention because of tubal rupture[27]. This suggested a great promise for this relatively new mode of treatment, however, the best method of MIX therapy is still being debated.

Modes of MIX treatment

In the treatment of ectopic pregnancy, MIXis given in several ways. Each mode of therapy has its advantages and disadvantages.

1. Systemic administration

This treatment was adopted in the very first trials of MIX therapy in ectopic pregnancy[17,21,23,24,28-30]. The anti-folate could be administered either intramuscularly or intravenously with or without citrovorum factor. Two reports pertaining to the treatment of unruptured tubal gestations with MIX are significant in this regard[20-24]. In one of these reports, Ichinoe et al. in 1987 treated 23 patients with intramuscular injections of MIX (0.4 mg/kg/day for 5 days) every other week until the urinary hCG levels dropped to 20 mIU/ml and achieved resolution of ectopic gestation in 22 patients within 6-47 days[20]. Patency of the oviducts was established in 53% of the cases. Except for some changes in liver function tests and slight bone marrow suppression, no untoward side effects were noticed. In another study, Saueretal. in 1987 treated 21 patients with unruptured tubal pregnancy with a single course of 4 intramuscular injections of MIX (1 mg/kg on day 1,3, 5 and 7 after laparoscopy) followed by intramuscular injections of citrovorum factor (0.1 mg/kg on day 2,4,6 and 8 after laparoscopy)24. All ectopic pregnancies except one with intra-abdominal bleeding resolved without surgery within 5-60 days (median time for resolution was 27 days). Seventy-five percent of the patients (15 out of 20) had patent tubes as revealed by HSG. Five out of the 21 patients showed symptoms of mild toxicity (stomatitis, pleuritis and mildnausea) which resolved within 4 days of therapy termination. One of the patients, in whom fetal heart activity was demonstrated by ultrasound, required laparotomy after MIX treatment as bleeding started in her at the placental site. Therefore, it was concluded that ectopic pregnancies that form fetal elements should not be managed medically. In remaining patients elimination of major surgery and demonstration of tubal patency were the principal benefits of this therapy. Recently, Stovall et al. have reported somewhat better results on a larger group of patients (n = 36) [23]. These patients with unruptured tubal pregnancy were treated with MIX-citrovorum factor protocol similar to the one used by Sauer et al. [24]. However, they used individual dosage regimen based on hCG and serum progesterone titers. This greatly reduced the total dose of chemotherapy required. Due to this, the incidence of chemotherapeutic side effects was substantially reduced. Only one of 36 patients developed stomatitis which cleared within 24 hours after receiving the final dose of MIX.

Moreover hospitalization cost was significantly reduced as the patients were hospitalized only for laparoscopy, whereas the protocol by Sauer et al. required hospital stay for nearly 7 days. This improved regimen allowed patients to return to their normal schedules almost immediately. In all of the above mentioned reports, MIX was administered either intravenously or intramuscularly. Based on the success achieved by Barter et al. [31] in treating patients suffering from nonmetastatic gestational trophoblastic disease with oral MIX, Patsner and Kenigsberg successfully treated a case of ectopic pregnancy persisting after conservative tubal surgery with oral MIX therapy[32]. The drug was given in a dose of 0.4 mg/kg/day for 5 days. It was well tolerated and no change in complete blood count or liver function tests was observed. Stomatitis and mucositis did not occur and the patient became completely asymptomatic after 1 week of this treatment. The major advantage of this treatmentwas that it could be given in an outpatient setting.

2. Local administration

Reports of few cases of mild toxicity associated with systemic administration of MIX prompted gynaecologists to look for more specific treatment of ectopic pregnancy. One approach was to inject MIX directly into the gestational sac. The first report in this case appeared in 1987 when Feichtinger and Kemeter successfully managed ectopic pregnancy by injecting MIX into the pregnancy sac under vaginal ultrasound control[33]. More recently, Zakut et al. have treated ten patients with tubal pregnancy by injecting MIX (12.5 mg diluted in 1.5 ml of distilled water) into the gestational sac under direct laparoscopic vision followed by a dose of intramuscular MIX therapy (0.5 mg/kg) and folinic acid "rescue" (0.1 mg/kg) for 5 days[26]. Complete resolution of ectopics was achieved in 8 of these 10 patients within 6-47 days. Tubal patency was demonstrated in 100% (seven) of the cases examined by HSG. It was interesting to note that the two cases which did not respond to the treatment had ectopic pregnancy sac measuring 3 cm x 3 cm or more, whereas all of the responding cases except one had the sacs' size smaller than that. Moreover, these two patients who were not responding to MTX treatment had the highest hCG levels (3600 and 5700 mIU/ml) among the group suggesting that the size of the gestational sac and the initial hCG levels can be important parameters for determining the expected benefit of this therapy. Therefore, it appears that patients with large gestational sacs and with high initial levels of hCG should be treated surgically rather than with MDC. Another approach for local administration of MDC is injecting the thug (12.5 mg) directly into the fallopian tube. Pansky et al. have recently treated 27 patients with unruptured tubal pregnancy with a single injection of the drug into the ectopic site through the swollen tubal wall by means of a 15 cm long spinal needle (18 gauge) introduced under laparoscopic guidance[22]. Twenty-four of 27 patients responded to the treatment. Hospital stay was considerably shortened and administration of the drug in this manner probably facilitated achieving high tissue concentration of MDC in the affected tube, thereby avoiding the systemic route and reducing the risk of adverse reactions. Similarly, Risquez et al. in France have reported a novel procedure for intraluminal injection of MTX[34]. In this technique, selective retrograde transcervical salpingography was carried out for the diagnosis of ectopic pregnancy. Tubal catheterization not only facilitated the confirmation of the suspected tubal gestation but the therapeutic dose of MDC (5-35 mg) could also be injected into the lumen of the fallopian tube. All 4 patients treated this way had resolution of their ectopics. This simple procedure was well tolerated and there were no side effects. Quite recently, Kooi and Kock in Netherlands have successfully treated 25 patients with local MDC injection after vasoconstriction of mesosalpinx with adrenalin[27]. They selected a relatively high dose (100 mg) of the drug on the basis of reports that normal chorionic tissue is analogous to malignant trophoblastic tissue which has been known to be quite resistant to MTX[35]. In these patients, side effects of MDC and adrenaline were minimal. Whether this type of local treatment with the thug ensures better chances of fertility in future still remains to be tested. Leeton and Davidson in Australia followed a different approach for the management of ectopic pregnancy[25]. Under

ultrasound guidance, they punctured the amniotic sac with a 30 cm needle and aspirated the amniotic fluid in avolume of 10-12 ml. When the amniotic sac completely collapsed, 50 mg MDC was injected through the same needle into the sac in a volume of saline equal to the volume of the aspirate. This technique was similar to follicular aspiration and flushing often used in many in vitro fertilization oocyte-collection procedures[36]. Resorption and disorganization of the sac was noticed within two days of the procedure. Plasma hCG levels became very low (C 10 mIU/ml) within a month and a half. There were no symptoms of pain in the two patients treated this way. Spontaneous menstruation began in both of them within 6 weeks of the treatment.

Mechanism of action of MTX

MDC is a folate antagonist which inhibits the enzyme dihydrofolate reductase and, thereby, blocks the de novo pathway of DNA synthesis[37]. Through this effect the drug inhibits cell replication and hence exhibits its antitumor activity[38]. Since trophoblasts possess high proliferative activity due to increased levels of dihydrofolate reductase, they quickly respond to inhibition by MDC. There is no single explanation for the unique sensitivity of gestational trophoblastic tissue to this chemotherapy. Bagshawe has proposed a combination of logarithmic chemotherapy "kill" and tissue autodestruction as possible mechanisms[39]. Rapid doubling time and immunologic responses directed at paternal or other unique antigens are other factors that have received attention[40].

Concluding remarks

All these reports indicate a great promise for this newprocedure in the management of ectopic pregnancy. However, certain simple conclusions can be drawn from the published data. The most important among these is that the criteria for selection of patients for this therapy must be quite stringent as listed in Table I.

TABLE I. Criteria for selection of patients for methotrexate therapy.

1. No combination of intrauterine and extrauterine pregnancy[26,27].
2. An unruptured tube fully visualized at laparoscopy containing a mass indicative of an ectopic pregnancy[23-27].
3. No foetal heart activity[19,27].
4. Size of the ectopic not exceeding 3 cm in diameter[22-24,41].
5. Plasma hCG levels less than 10,000 mIU/ml[19,20].
6. No active bleeding in the peritoneal cavity[22-24,26,27].
7. A desire for pregnancy in the future[27].
8. Adequate follow up of a compliant patient[41,47].

Certain absolute contraindications to MDC therapy are given in Table II.

TABLE II. Contraindications to methotrexate therapy.

1. Rupture of ectopic pregnancy[14].
2. Size of gestational sac greater than 3 cm[41].
3. Presence of cardiac activity[19,24,41].
4. Unstable vital signs[19].
5. History of active hepatic or renal disease[19,23,41].
6. Abnormal blood urea, nitrogen, serum creatinine or serum glutamic-oxaloacetic transaminase levels[19,23].
7. Proteinuria[19].
8. Methotrexate sensitivity[19].
9. Active peptic ulcer disease[19]
10. A white blood count of 3,000/mm^3, a platelet count of less than 10,000/mm^3 or a hemoglobin of less than 11 gm/dl[19].
11. Poor patient compliance and follow up[19,41,48].

It is noteworthy that the treatment has been possible only because of early detection of ectopic gestations due to recent advances in diagnostic modalities. Moreover, the treatment when carried out judiciously is quite effective and has minimal side effects and toxicity. When compared to the traditional surgical procedures, there appears to be a better reproductive performance after this therapy[41]. Selected cases of cornual or cervical pregnancy or those with residual trophoblastic tissue which are usually difficult to manage surgically are good candidates for MDC therapy[28,42-45]. It is cost effective in terms of reduction in hospitalization and convalescence time. It should be emphasized that inspite of all its merits, MDC therapy appears appropriate for a select group of patients who fulfil certain criteria and that surgery would still be mandatory when there is a risk of tubal rupture or when intra-abdominal bleeding has taken place. In third world countries where catastrophic presentation of a ruptured ectoyic gestation and hemoperitoneum is quite common surgery may still remain the major treatment. Nevertheless, with the availability of ultrasound facility especially with the introduction of vaginal probe and sensitive assay systems for hCG in major hospitals, it has now been possible to diagnose this condition before a rupture occurs while the patient is only minimally symptomatic. Accordingly, the treatment of ectopic pregnancy may shift from an immediate life saving intervention into a more conservative method of management, aimed primarily at presenting fertility and reducing the morbidity[41]. Use of MDC is one of these new conservative approaches which may achieve that objective.

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REFERENCES

1. clayton, Sfl., Lewis, T.LT. and Pinker, 0. Obstetrics. 14th ed. London, Arnold, 1985; pp. 115-9.
2. Ectopic pregnancy- United States, 1981-1983. M.M.W.R, 1986; 35:289.
3. Ectopic pregnancies- United States, 1979-1980. M.M.W.R., 1984; 33:201-2.
4. kadar, N. Ectopic pregnancy; a re-appraisal of aetiology, diagnosis and treatment, in progreaa in obstetrics and gynaecology. Edited by i. Studd. London, Churchill Livingston; 1983; vol.3, pp. 305-23.
5. Tait, R.L. Pathology and treatment of extra-uterine pregnancy. Br. Med. J., 1984; 2:317-23
6. Stromme, WSSalpingostomyforectopicpregnancy: reportofa successful case. Am.J. Obstet. Gynecol., 1953; 87:757.
7. Stromme, WB. Conservative surgery for ectopic pregnancy. Obstet. Gynecol. 1973; 40:709-23.
8. Pouly, it, Mahnes, H., Mage, 0., Canis, M. and Bruhat, M.A. Conservative laparoacopic treatment of 321 ectopic pregnancies. Fertil. Steril., 1986; 46:1093-7.
9. Hallatt, J.G. Tubal conservation in ectopicpregnsncy; a study of 200 cases Am.i. Obstet. Gynecol., 1986; 154:1216-21.
10. Vermesh, M. Conservative management of ectopic gestation. Fertil. Steril., 1989; 51:559-67.
12. Kamrava, M.M., Tsymor, M.L., Bcrger, M.J., Thompson, I.E. and Seibel, M.M. Disappearance of human chorionicgonadotropin followingremovalofectopicpregnan cy. Obstet. Gynecol., 1983; 62.486-8.
12. Rivlin, M.E., Merits, OAt, Cowan, B.D. and Bates, G.W. Persistent trophoblastic tissue following salpingostomy for unruptured ectopicpregnancy. Fertil.Steril, 1985; 43:323-4.
13. Richards, B.C Persistent trophoblast following conservative operation for ectopic pregnancy. Am. 3. Obstet. Gynecol., 1984; 150:100.
14. Seifer, D.B., Guttman, J.N., Doyle, M.B., iones, E.E., Diamond, M.P. and Decherney, A.H. Persistent ectopicpregnsncy followinglaparoacopic linearsslpingostomy. Obstet Gynecol., 1990 76:1121-5.
15. Lundorff, it, Hahlin, M., Sjoblom, P. and Lindblom, B. Persistent trophoblast after conservative trestment of tubal pregnancy: Prediction and detection. Obster. Gynecol, 1991; 77:129-133.
16. Homesley H.D., Blessing, J.A., Rettenmaier, M., Capizzi, R.L., Major, P3. and Twiggs, LB. Weekly intramuscular methotrexate for nonmetastatic gestational trophoblastic disease. Obstet. Gynecol., 1988; 72:413-7.
17. Tsnaks, T., Hayashi, H., Kutauzaws, t, Fujimoto, S. and lcbinoe, K Treatment of interstitial pregnancywith metbotrexate; reportof a successful case. Fertil. Steril., 1982;37:851-2.
18. Miyazaki, Y., Shims, Y., Wake,N., Okado, Y., Yamazaki, H.,Takeds,W. and febinoe, K. Studies on non-surgical therapy of tubal pregnancy. Nippon Sanka Funinka Gakkai Zssahi (Acts. Obstet. Gynecol. Jpn.). 1983; 35:489-92.
19. Ory, Si., Villanueva, AL, Sand, P.K and Tamurs, R.K. Conservative treatment of ectopic pregnancywitb methotrexate. Am.). ObsteL Gynecol., 1986; 154:1299-1306.
20. Ichinoe, K, Wake, N., Shinkai, N., Shims, Y., Miyazaki, Y. and Tanaka, T. Nonsurgical therapy to preserve oviduct function in patients with tubal pregnancies. Am.J. Obstet. Gynecol., 1987; 157:484-87.
21. Rodi, LA., Sauer, Mv., Gorrill, Mi., Bustillo, M., Gunning, I.E., Marshall, 3.8.. and Buster, I.E. The medical management of unruptured ectopic pregnancy with metbotrexste and citrovorum rescue: preliminary experience. Fertit Steril., 1986; 46:811-13.
22. Pansky. M., Bukovsky, L, Golan, A, Langer, 8.., Schneider, D., Arieli, S. and Caspi, E. Local methotrexate injection; a nonsurgical treatment of ectopic pregnancy. Am. J. Obstet. Gynecol., 1989;

161:393-6.
23. Stovall, T.G., Ling, F.W. and Buster, I.E. Outpatient chemotherapy of unruptured ectopic pregnancy. Fertil. SteriL, 1989; 51:435-8.
24. Sauer, M.V., Gorrill, Mi., Rodi, LA, Yeko, T.R., Greenberg, LH., Bustillo, M., Gunning, i.E. and Buster, I.E. Nonsurgical management of unruptured ectopic pregnancy: an extended clinical trial. Fertil. Steril., 1987; 48:752-55.
25. Leeton, 3. and Davison, 0. Nonsurgical management of unruptured tubal pregnancy with intra-amniotic netbotrexste: preliminary report of two cases. Fertil Steril., 1988; 50: 167-9.
26. Zakut, H., Sadan, 0., Katz, A, Dreval, D. and Bernstein, D. Management of tubal pregnancywith metbotrexate. Br.i. Obstet. Gynaecol., 1989: 96:725-8.
27. Kooi, S. and Kock, H.C.L.V. Treatment of tubal pregnancy by local injection of methotrexate after adrenaline injection into the mesosalpinr a report of 25 patients. Fertil. Steril., 1990; 54:580-4.
28. Brandes, M.C., Youngs, D.D., Goldstein, D.P. and Psrmley, T.H.Trestment of cornual pregnancywith methotrexate: case report. Am.). Obstet. Gynecol., 1986; 155:655-7.
29. Cowan, B.D., McGehee, R.P. and Bates, G.W. Treatment of persistent ectopic pregnancy with methotrexate and leucovorin rescue: case report. Obater. Gynecol., 1986; 67:50(S)-SI(S).
30. Higgins, KA. and Schwartz, MB. Treatment of persistent trophoblastic tissue after salpingostomy with methotrexate. Fertil. Steril., 1986; 45:427-8.
31. Barter, J.F., Soong. S.J., Hatch, K.D., Orr, J.W. Jr., Partridge E.C., Austin, J.M. Jr. and Shingleton, H.M. Treatment of non- metastatic gestational trophoblassic disease with oral methotrexate. Am.). ObsteL Gynecol., 1987; 157:1166-8.
32. Patsner, B. and Kenigsberg. D. Successful treatment of persistent ectopic pregnancy with oral methotrexate therapy. Fertil. SteriL 1988; 50:982-3.
33. Feicbtinger, W. and Kemeter, W. Conservative treatment of ectopic pregnancy by trsnsvaginal aspiration under sonographic control and methotrexate injection (letter). Lancer, 1987; 1:381-2.
34. Risquez, F., Mathieson, J., Pariente, D., Foulot, H., Dubuisson,).B., Bonnin, A, Cedard, Land Zorn, J.R. Diagnosis and treatment of ectopic pregnancy by retrograde selective salpingography and intraluminal methotrexate injection: work in progress. Hum. Reprod.. 1990; 5:759-62.
35. Sand, P.K., Stubblefield, P.A and Ory, Si. Methotrexate inhibition of normal trophoblaste invitro. Am.). Obstes. GynecoL, 1986; 155;324-8.
36. Lenz, S., Leton, J. and Renou, P. Trsnsvaginal recovery of oocytes for in vitro fertilization usingvaginsl ultrasound.). In vitro. Fert. Embryo. Transfer., 1987; 4:51-5.
37. Bertino, J.R. The mechanism of action of the folate antagonists in man. Cancer Res., 1963; 23: 1286-1306.
38. Jolivet, J., Cowan, K.H., Curt, GA., Clendeninn, Ni. and Chabner, B.A. The pharmacology and clinical uscof methotrexate. N. Engl.J. Med., 1983; 308.1094-1104.
39. Bsgshswe, K.D. Tumour growth and anti-mitotic action. The role of spontaneous cell losses. Br.). Cancer, 1968; 12:698-713.
40. Freedman, ItS. Methotrexate in gestational trophoblastic disease, Cancer BulL, 1981; 33:63-6.
41. Stovall,T.G., Ling, F.W. and Buster,),E. Reproductive performancesftermethosrexate treatment ofectopic pregnancy. Am.). Obstet. Gynecol., 1990; 162:1620-24.
42. Stovall, T.G., Felker, R., Ling, F.W., Raso, B.J., Smitch, W.C. and Buster, J.E, Successful nonsurgical treatment of cervical pregnancy with methotrexate. Fertil. Steril., 1988; 50:672-4.
43. Oyer, it, Tarskjian, D., Lev-Toaff, A, Friedman, A and Chstwani, A Treatment of cervical pregnancywith methotrexate. Obstet GynecoL, 1988; 71:469-71.
44. Farsbow, W.S., Fulton,).W., Fletcher, V. Jr., Velat, C.A and White, J.A. Cervical pregnancy treatedwith methotrexate. N.C. Med.)., 1983; 44:91-3.
45. DeCherney,AH. and Dismond, M.P. Laparoscopic salpingostomy for ectopic pregnancy. Obstet. GynecoL, 1987; 70:948-50.

46.Malik, Lit Autotrsnsfusion in ruptured tubal pregnancy. J.Pak. Med. Assoc., 1987; 37:78-9.
47. Blackwell, B. Drug therapy; patient compliance. N. Engl. J. Med., 1973; 289.249-52
48. Lebovits, A.H., Strain, J.J., Schleifer, Si., Tanaka, J.S., Bhardwaj, S. and Messe, M.R. Patient noncompliancewith self- administered chemotherapy. Cancer, 1990; 65:17-22.