MODULATION OF NATURAL KILLER CELL ACTIVITY AS A POSSIBLE CONJUNCTIVE METHOD IN TREATMENT OF OVARIAN CARCINOMA UTILIZING MGN-3, A MODIFIED XYLOSE FROM RICE BRAN (CASE REPORT)

Mamdooh Ghoneum1, Gus Gill1, Departments of Otolaryngology-Head and Neck Surgery, and Pathology Drew University of Medicine and Science 1621 East 120th Street, Los Angeles, CA 90059

1. CLINICAL HISTORY: The patient is a 53 year old female who was diagnosed as having ovarian carcinoma on February 11, 1993. Clinical symptoms included swelling of the breast and abdominal distention. Past history revealed no serious illness.

2. PHYSICAL EXAMINATION: The most significant positive findings of the physical examination were swelling of the breast and abdominal distention. The remainder of the physical findings were within normal limits.

3. LABORATORY DATA: Abdominal ultrasound and CT scan revealed changes compatible with ascitis. RMI results were highly suggestive of ovarian carcinoma with ascitis. CA 125 was 327 U/ml.

The patient underwent an exploratory laparotomy debulking procedure including; total abdominal hysterectomy, bilateral salpingo- oophorectomy, omentectomy and lymphnode dissection. Subsequently, the patient was started on chemotherapy consisting of cysplatin

and 5 FU

CBC: Within normal limits.

Chemistry: Within normal limits.

4. PATHOLOGICAL FINDINGS: High-grade serous papillary cyst adenocarcinoma with areas of undifferentiation and frequent mitosis. Tumor involved both ovaries with multiple peritoneal implants. Lymphnodes were free of tumor. Cytospin and button section peritoneal fluid showed malignant cells.

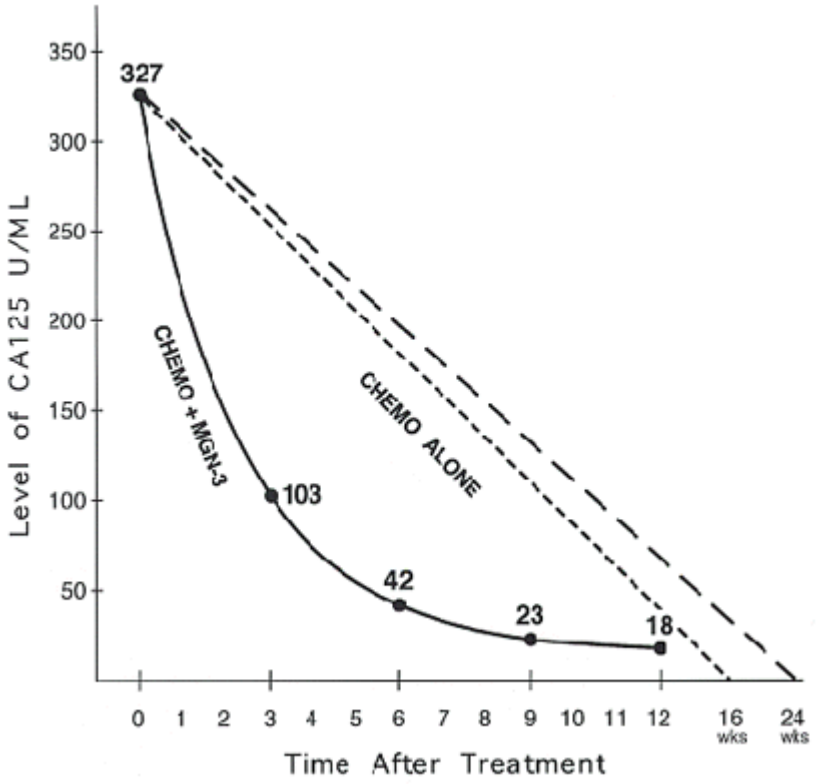
5. TREATMENT: Following surgery, the patient underwent a course of chemotherapy consisting of cysplatin and 5 FU. MGN-3 (3gm/d) was given orally by mouth in concurrence with the chemotherapy. The patient's progress was monitored by sequential determinations of CA 125.

6. MGN-3: MGN-3 is a xylose from rice bran that has been modified enzymatically by culture with Hyphomycetes mycelia. It is a polysaccaride that contains B1,4 xylopyronase hemicellulose and glycoprotein. MGN-3 was prepared in the form of capsules. Ingredients (per capsule) are 400 mg MGN-3 plus 100 mg vegetable oil. MGN-3 was produced, and provided by Daiwa pharmaceutical Co., LTD., Tokyo,Japan.

7. METHODS: NK cell activity was examined by standard 4-hr 51cr-release assay. K562 tumor cells were used as targets and NK activity was assayed at different effector:target (E:T) ratios = 12:1, 25:1, and 50:1. Results were expressed as number of lytic units (LU) at 20%.

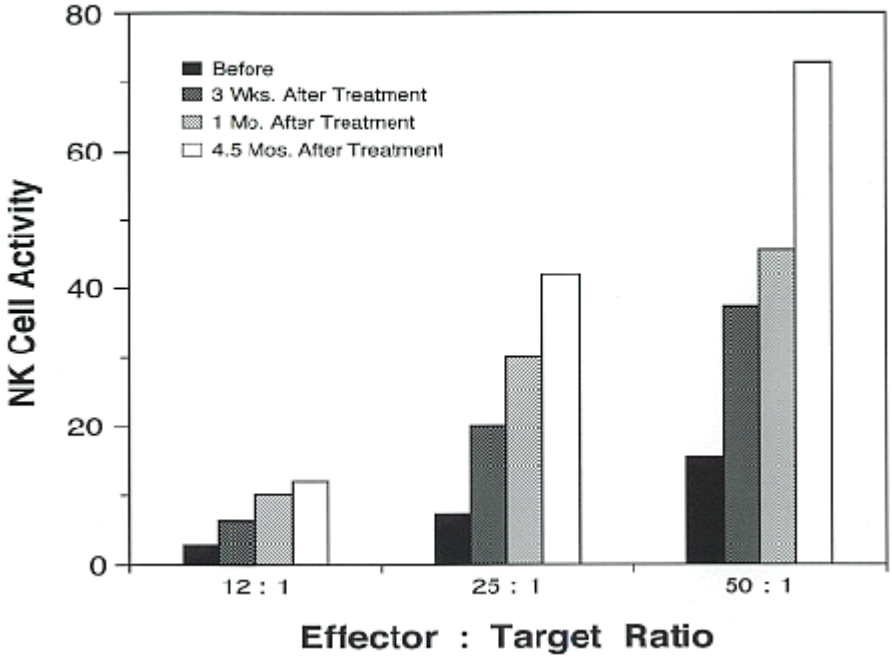
8. RESULTS:

A. Levels of CA 125: The baseline of CA 125 post surgery was 327 U/ml. A significant reduction in the level of CA 125 (60%) was noticed at 3 wks post treatment of chemotherapy in concurrence with MGN-3, and further reduction in CA 125 value was noticed at 6 wks after treatment where the level of the antigen reached that of controls (0-35 U/ml). CA 125 was maintained at low level in the subsequent examination; 23 and 18 U/ml at 9 and 12 wks post treatment. Respectively (Fig.1).



B. <u>NK Cell Activity</u>: Baseline of NK cell activity of the patient demonstrated 2.9, 7.4, and 15.2% at E:T ratios = 12:1, 25:1, and 50:1 respectively. NK activity was further examined at different intervals post treatment with chemotherapy in conjunction with MGN-3. Results showed a significant enhancement in NK activity as early as 3 wks after treatment. An increase in NK activity was observed at all E:T ratios as follows: 6.6% at 12:1, 20.2% at 25:1 and 37.4% at 50:1. NK activity was maintained at a high level at 1 month after treatment and further increase in activity was observed at 4.5 month; 11.7, 41.1, and 72.6 at 12:1, 25:1, and 50:1 respectively. (Fig. 2)

Fig. 2



C. <u>FLOW CYTOMETRY STUDY</u>: Flow cytometry study was used to evaluate the percentage of CD56+ cells. Results showed no significant change in NK cells post treatment as compared to NK cells before treatment. (Table 1).

Table 1

Time (Months)	$CD56^+$	$CD3^+$	$CD3^-$
0	11.5	4.2	7.3
1	12.5	4.2	8.3
4.5	13.8	4.3	9.5

CONCLUSION

In this study we reported that a patient with ovarian carcinoma who received a combination of chemotherapy with concurrent use of MGN-3 resulted in shortening of period to achieve complete clinical remission in two months. Average patients with cystadenoma takes up 3-4 months for normalization when treated with chemotherapy alone.

MGN-3 effect may be through NK immunomodulation. Natural killer (NK) cells have the ability to mediate natural resistance against tumors, and play an important role in immune surveillance (1-5). A significant enhancement of NK cytotoxicity was noticed at 3 wks post treatment and maintained at high level up to 4.5 months. An increase in NK cytotoxicity was independent of NK cell number as measured by flow cytometry suggesting that MGN-3 increase NK cytotoxicity per se. Results of this study suggesting that MGN-3 increase NK cytotoxicity per se. Results of this study suggest a possible uracil role of MGN-3 as conjunctive therapy in the treatment of ovarian cancer.

The observed increase in NK activity of the patient post treatment with MGN-3 suggests that MGN-3 is a potent biological response modifier (BRM) which can counteract the immunosuppressive effect by chemo. Several studies clearly showed that chemotherapeutic agents are immunodepressants. Chemotherapeutic drugs may cause a reduction in the actual number of immune cells or a direct inhibition of their effector function (6). Patients receiving cisplatin had 8-16-fold reduction in NK activity at 15 days post treatment. Similarly cisplatin-treated mice had a reduced level of NK activity that was first apparent 8 days post treatment and reached a nadir on day 15. Both patients and murine NK activities returned to normal level at 3 wks (7). A marked reduction in NK activity could be detected as early as 24 hr. after treatment with cisplatin in the presence of dexamethasone- a drug used as an antiemetic to prevent nausea (8). Patient is doing extremely well and remained clinically disease-free, possibly due to crucial role of MGN-3 as conjunctive therapy in treatment of ovarian cancer. Multiple clinical trials is needed to examine the role of MGN-3 as conjunctive therapy in the treatment of ovarian cancer and confirm the hypothesis of shortening of the period of clinical remission during chemotherapy by MGN-3.

References:

1. Ghoneum, M., K. Jackson, F. Salem and G. Gill. 1991. Murine intersex difference in methylcholanthrene induced tumor and its correlation with NK activity. Int. J. Immunopathol.Pharmacol. 4:9.

2. Ghoenum, M.F. Salem, G.Gill, K. Jackson, Y. Betru, and H. Allen 1989. NK cell activity and tumor development of age-related variation to 3-methylcholanthrene. In:Ades EW, Lopes G. eds. Natural killer Cells and Host Defense, Basel: Karger pp, 278-84.

3. Herberman RB 1983. Possible role of natural killer cells in host resistance against tumors and diseases. Clin. Immun Allergy, 3:479.

4. Jondal M. 1987: The human NK cell-a short over-view and an hypothesis on NK recognition. Clin Exp Immunol, 70:255.

5. Roder J.C., and H.F. Pross: (1983) The biology of human natural killer cell. J. Clin. Immun. 2:249.

6. Colv. The alkylating agents. In Pharmacologic Principles of Cancer. (ed. by D. Chabner & B. Bruce) p. 980. W.B. Saunders.

7. Powell, C.B., M ntiemetic in inhibits natural cytotoxic (NC) activity. Cancer, 65,80. (1990a)

8. Powell CB, Mutch DG, Kao MS and Collins JL. Reduced natural cytotoxic cell activity in patients receiving cisplatin-bared chemotherapy and in mice treated with cisplatin.Clin. Exp. Immunol. 79,424 (1990b).

MG:ovarian