MITOMYCIN C in clinical oncology

KYOWA HAKKO KOGYO CO., LTD.

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KYOWA HAKKO KOGYO Co., Ltd. Otemachi Bldg., 1-6-1 Otemachi, Chiyoda-ku, Tokyo (100)

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Introductory Remarks MAKOTO OGAWA, M.D.

Asian-Pacific International Symposium of Mitomycin C was held in December 1979 in Bombay, India, during The Fourth Asian Cancer Conference.

Mitomycin C is an old drug which was discovered by Hata and co-workers^{1,2)} in 1955 and Japanese clinical trials³⁾ were initiated in 1957 using intravenous daily dosages ranging from 1.0 to 4.0 mg/body, thereafter, during early 1960's several investigators in other countries initiated clinical study of mitomycin C. So that mitomycin C has been clinical studies for more than a quarter of century.

However, until recently the drug had been known to have rather limited clinical activity in association with delayed and cumulative hematologic toxicity. Since this hematologic toxicity has been overcome by intermittent schedules and the drug has proven significant activities in gastric cancer and other tumors, the renaissance of mitomycin C in cancer chemotherapy has emerged.

The drug has proved significant clinical activities in gastrointestinal tumors, breast cancer, lung cancer, genitourinary tumors and gynecologic tumors.

In this book eleven oncologists joined to the symposium from Asian Pacific countries describe recent developments of mitomycin C in cancer chemotherapy.

Chief, Division of Clinical Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo

REFERENCES

- 1) Hata, T., et al.: Mitomycin C, a new antibiotic from Streptomyces I. J. Antibiot. Ser. A., 9: 141-146, 1956.
- 2) Hata, T., et al.: Mitomycin C, a new antibiotic from Streptomyces II. ibid: 147-151, 1956.
- 3) Mitomycin C—Its experimental research and clinical application—. ed. by Shiba, S. and T. Taguchi, 1967, Igaku Shoin Ltd., Tokyo, Japan.

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Carcinoma of the Stomach and Mitomycin Chemotherapy. Analysis of 57 Cases.

MR. M.G. KULKARNI

SUMMARY

Fifty-seven personal cases of Carcinoma of the stomach treated with Surgery and Mitomycin Chemotherapy form the basis of this paper.

The material is analysed in terms of incidence, race, sex, age, distribution, duration of symptoms, physical findings, operation findings, pathology of tumour staging and follow up results.

Literature on Carcinoma of the stomach to highlight the Clinical problem is reviewed.

INTRODUCTION

OSLER'S TREATMENT OF CANCER OF THE STOMACH

In early Surgical Treatment lies the only hope, but there is great difficulty in the diagnosis and it would be absurd to suggest operation in every case of dyspepsia of three months standing in persons above forty years of age. Operated upon early, complete removal is sometimes possible. In majority of cases the operation is only palliative. In suitable cases early exploration should be advised; the operation per/se is sometimes beneficial and the patient is rarely the worse for it. The diet should consist of readily digested substances of all

Hospital Queen Elizabeth, Kota Kinabalu

Table 1. Cancer of the stomach, stastics from West Malaysia (I.M.R) 1972 to 1976/Sabah 1969 to 1977.

Centre	incidence (%) per 10,000 popn	sex ratio		Total
Imr (kl)	per annum	Chinese:	2:1	292
1972-76	5.9	Malays:	1:1	
		Indians:	3:1	
		others:	1:3	
Sabah (oeh,kk)	5.4	Chinese:	2:1	170
1969-1976		Kadazans:	2:1	
		Malay:	2:1	

- 1) Kadazans predominantly affected
- 2) Increasing incidence due to:
 - i) Improved detection and clinical and surgical confirmation
 - ii) Pathological confirmation
 - ii) Documentation
 - iv) Notification

Table 2. Symptoms and Physical signs.

Symptoms	No. of Patients	Percentage (%)
Epigastric discomfort	35	85
Epigastric pain	33	83
Loss of weight	32	80
Loss of appetite	30	73
Anorexia	20	50
Vomiting	19	49
Tarry stool	14	34
Dysphagia	5	12
Signs	No. of Patients	Percentage (%)
Anemia	27	61
Upper abd mass	21	51
Hepatomegaly	6	15
Ascites	5	12
Pelvic mass	4	10
Jaundice	0	0
Supraclavicular nodes	9	22
	Total No. of	Patients=41

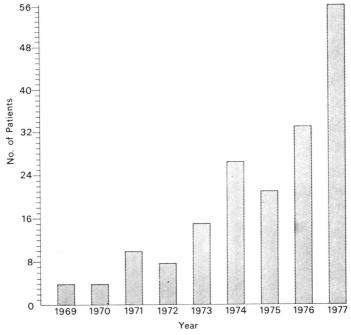


Fig. 1. Yearly detection of Cancer of the Stomach in Sabah 1969-1977.

sorts. Many patients do well on milk alone. Washing out of the stomach which may be done with a soft tube without risk is particularly advantageous when there is obstruction at the pylorus, and is by for the most satisfactory means of combating vomiting. The excessive fermentation is also best treated with lavage. When pain becomes severe, particularly if disturbs the rest at night Morphia must be given 1/8 gr combined with Carbonate of soda (gr r) Bismuth (gr x) usually gives prompt relief, the dose does not require to be increased, Creasote (msii) carbolic acid are very useful. The bleeding Cancer is rarely amenable to treatment. Even in 19th century Carcinoma of the stomach poses Acute problem of early detection, Surgical management and understanding the scope and limitations of curative, palliative

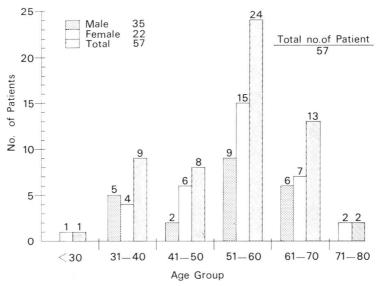


Fig. 2. Sex and Age Distribution of Cancer of the Stomach in 57 cases.

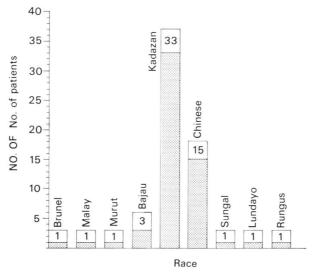


Fig. 3. Racial Distribution.

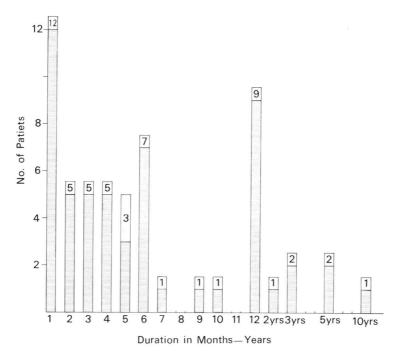


Fig. 4. Duration of Symptoms.

Table 3. Site of Cancer in Stomach.

Site	No. of Patients	% Occurence
Lesser curvature	17	43
Prepyloric antrum	16	41
Cardia	4	10
Greater curvature	2	6
No records traceable	13	
Clinical diagnosis	5	
Total No. Patients	57	39

resections, chemotheraputic treatment, assessment and analysis of results.

Early diagnosis which governs prognosis in terms of 5 to 10 year survival still eludes Clinician and surgeons mainly due to variable

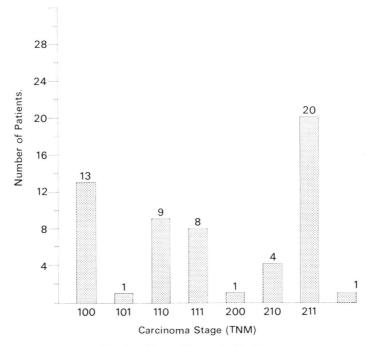


Fig. 5. Stages Cancer in 57 Cases.

symptoms, limitations of investigations and their interpretations and surgical treatment. Five year survival rate from various centres falls in the range of 19-35% which stresses the situation adequately.

Emerging from this assay, more concentrated effort on Early diagnosis and Radical Resections combined with Chemotherapy offer better prospects of long term symptom free survival than one modality of treatment alone.

DISCUSSION

Even in Sabah, Carcinoma of the Stomach is the third most common Cancer with high mortality rate, 50–60 cases per annum or 0.56/10,000 population is the average incidence.

condition of patients	No. of patients	percentage
Asymptomatic	11	39
normal appetite no loss of weight Poor appetite abdominal pain loss of weight	7	25
Terminal cases	4	14
Expired from desseminated cancer	6	22
Total No. of Patients	28	

Table 4. Results of Mitomycin chemotherapy and Follow up Results.

MALE

Female ratio of 2: 1 is similar to one noted in the Western world (Cassell's, Robinson 1976) 45 out of 57 cases in our series were between 41-70 years age (66.2% in Cassell's series between 50-70 years).

RACIAL

Distribution may be contrary to that noted in Singapore or Hong Kong. Kadazans exceed Chinese 33 against 15 while other races incidence is low.

Shortest duration of symptoms noted was 1 month and the longest being 10 years. Majority (37 cases) were below 6 months, 12 below 1 year and 6 between 2–10 year. This finding is similar to one noted in Cassel's Series of 857 Cases.

80-85% of our series had Epigastric Pain and loss of weight, vomiting in 49%, malaena in 34% and dysphagia in 12%. 61% had anaemia and abdominal mass in 51%, respectively, supraclavicular nodes in 22%. Hepatomegaly in 15%, ascitis in 12%, Pelvic Mass in 10% but jaundice in none.

BASED

On: T, N, M, classification only 13 cases were in $T_1N_0M_0$. $T_2N_0M_0$, 1, $T_1N_1M_0$, 9, $T_1N_1M_1$, 8, $T_1N_0M_1$, 1, $T_2N_0M_1$, 1, $T_2N_1M_0$, 4 and $T_2N_1M_1$, 20.

This stresses the crucial point of diagnosis, management and role of Mitomycin Chemotherapy. Majority of cases fall in the category of *Palliative Resection*. Our operability rate was 100% as compared to other countries of 79 to 90% (Cassel's) resectability rate of 30% comparable to other countires figure of 37–52%.

In our series lesser curve lesion was noted in 43%. Pyloric antrum 41%, Greater Curve in 6%, Cardia in 10% in contrast to Cassel's series Body 35%. Pyloric 29%, Fundus 16%, Extensive Cancer 13%, leather bottle is 7%.

Ulcerating lesions exceeded polypoid growth and moderate to undifferentiated adeno carcinomas exceeding well differentiated cancer of the stomach.

Mortality rate of cancer of the stomach varies with the surgical procedure—highest in irresectable growth 19.6% to Laparotomy and by pass 16.6%. Total gastrectomy having higher mortality than partial gastrectomy.

Survival rate also is dependent on the procedure undertaken. Remine & Priestley (1966) from Mayo Clinic quote a figure of 34%, Hawly (1970) 19.4% for 5 years and 11.5% for 10 years from UK.

In view of the stage of cancer of the stomach reaching surgical unit, difficulties in assessing tumour stage at operation and appreciating the limitation of term curative and palliative resections, definitive policy was adopted in treating all cancer of the stomach patients, irrespective of staging.

- 1. All patients were given per-operative Mitomycin 10 mg IV with B6 200 mg.
- 2. All patients were subjected to Laparotomy and histological confirmation obtained.
- 3. Resection by partial or total gastrectomy undertaken in all resectable cancers with intra-operative Mitomycin 10 mg I.V.

- 4. Post operative Mitomycin was continued as long as 6 months to a year.
- 5. With few exceptions, all patients were followed up regularly in Cancer Clinic.
- 6. Subjective feeling to improvement by way of increase in weight appetite, lack of pain, objective signs of decrease in size of epigastric mass, hepatomegaly and other obvious secondaries were documented.
- 7. Blood and Hepatic function were monitored, Low dose, prolonged Mitomycin therapy was chosen so as to minimize toxic side effects. This was in contrast to high doses short course therapy. (17.5 mg per day Frank and Ostenberg) (50 mg/kg Body? daily for 6 days Ausman Method).

The results were analysed. 39%: —

- 1. Were asymptomatic and returned to normal life.
- 2. Relapsed after initial good response with abdominal pain and loss of weight 25%.
- 3. Terminal cases with poor response to therapy 14%.
- 4. Expired due to dessiminated Cancer 22%.

Longest follow up of this series is over 2 years and 39% of cases are on record leading a normal life. Of the 25% who showed initial good response for 6 to 12 months before succumbing to Cancer dessimination, majority had $T_2N_1M_0$ Stage Cancer of the Stomach. The quality of life has been very much better in contrast to untreated cases.

Irresectable carcinoma of the Stomach who had bypass operation also had extensive hepatic secondaries all died within a year of laparotomy. This constituted 14% of the series.

Allowing for the fact that the mumber in the series is small and follow up period not edequate enough to be dogmatic, it is promising to note that 39% of the cases are able to lead a normal life, beyond 2 years, period.

It is through perseverance and repeated evaluation of one's techniques we may be able to treat Cancer of the Stomach early and adequately to achieve the objective cure.

REFERENCES

- Cancer of the Stomach: —A review of 854 patients. Cassell P. Robinson, J.B. J.S. Vol. 63 (1976), 603-607.
- Carcinoma of the Stomach, Philadelphia Saunders Remine W.H. (1964 a).
- 3. W. Osler, The Principles & Practice of Medicine Ed 7, New York D. Appleton, & Co. 1911. p. 486).
- Mitomycin, C. Therapy in Advanced Gastro-Intestinal Cancer. Moertel, C.G., Reitemeier, J., Hahn, R. JAMA, June 17th 1968, Vol. 204 No. 12. Trends in Prognosis and Surgical Treatment of Cancer of the Stomach. Remine, W.H., Prestley, J.T. (1966) Ann. Surg. 163, 736-745.
- 5. An evaluation of the Japanese Report Mitomycin, C. Cancer Chemotherapy Rep. 9-114-119 (November) 1960.
- 6. Pathology and Prognosis of Carcinoma of the Stomach. Hawley, P.R., Westerholm, P., Morson, B.C. (1970) B.J.S. 57, 877-883.