Cancer Chemother Pharmacol (1982) 8: 231–235

Cancer Chemotherapy and Pharmacology

Primary Hepatocellular Carcinoma

Present State of the Disease and Prospects for the Future

Chong-Jin Oon[1] and Michael A. Friedman[2]

[1] Division of Oncology and Immunology, University Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316
[2] Cancer Research Institute, 1282-M, University of California, San Francisco, CA 94143, USA

Summary. *Primary hepatocellular cancer is a common and virulent malignancy found all over the world. New insights into this disease are being provided by evaluation of the impact of epidemiologic data (hepatitis viral exposure, race, sex, HLA typing, and environmental factors). An enhanced appreciation of the biochemical modulators of hepatocellular cancer metabolism is now also possible. The limited success of current therapies is far from satisfactory, but prospects for the future seem more varied and promising than ever before.*

Epidemiologic Factors

Primary hepatocellular carcinoma (PHC) is an almost uniformly fatal primary hepatic malignancy responsible for the death of an estimated 1 million people annually. The incidence of the disease, based on data available from national cancer registries, ranges from 2 to 104 per 100,000 (age-standardized to world population) [14]. In many areas where no formal cancer registries exist, collaborative reports from cancer institutes or hospitals give some indication of the incidence of this disease, and it is especially frequent in parts of Africa and in North and Southeast Asian countries [25, 34]. Additionally, a high rate of occurrence has been reported in indigenous races living in disparate parts of the Pacific basin, such as Polynesia [22], New Guinea, and Alaska [2].

Hepatitis B Infection and PHC

Because of the high incidence of PHC in certain geographic areas, an intense interest has been sustained in identifying specific epidemiologic factors. Most probably, the etiology of PHC is multifactorial. The regenerating, damaged liver seems to be most susceptible to this malignancy, and currently the greatest interest focuses on the relationship between hepatitis B infection and PHC. In one highly endemic area in Jiangxu province in China, the incidence of the disease was 50.7 per 100,000 and was closely associated with a high incidence of hepatitis B infection (HBsAg) in the population (data from Singapore Cancer Registry, by courtesy of Prof. K. Shanmugaratnam). In many Asian-Pacific and African countries where the carrier state for HBsAg is high, the incidence of PHC is similarly high. The association between PHC and seropositive HBsAg varies from 60% to 95%, and prolonged HBsAg infection appears to play an important role in the development of PHC, as confirmed in prospective studies on HBsAg-positive carrier populations in Taiwan [1] and other countries [26, 32, 37]. Cirrhosis, often occult, is associated with PHC [25] and shows an association with this virus [32]. In contrast, PHC seen in the Caucasian population in many Western countries is more often related to post-alcoholic cirrhosis, suggesting that several types of hepatic injury may predispose to PHC.

Non-A and non-B viruses also produce similar hepatic damage and cirrhosis to those produced by hepatitis B viruses. It would therefore be of equal importance to assess their significance in the pathogenesis of PHC in endemic regions of the world.

Nutritional Factors

In particular areas of the world, various ingested mycotoxins [5, 28] and nutritional factors may have an important etiologic role. If dietary (or other nonviral) causes are not at least partially responsible,

Reprint requests should be addressed to M. A. Friedman

0344-5704/82/0008/0231/$ 01.00

it is difficult to explain why there is a high incidence of PHC in Alaskan Eskimos, especially since a carrier rate of HBsAg of only 12% has been reported in this population [2].

Race and Environmental Carcinogesis

Race has been correlated with environmental factors in Singapore's epidemiological studies on the incidence of PHC. Whereas the Indians living in Singapore had the highest morbidity rate for acute viral hepatitis (type B), exceeding that of the Chinese by 1.3 times [13], the incidence of PHC was considerably lower in Indians than in the Chinese population. Nevertheless, Indians living in Singapore and South Africa (who have a relatively high incidence of primary liver cancer) exhibited a higher frequency of PHC than Indians living in India. Studies on Singapore Chinese PHC patients show some clustering of individuals who have the HLA B5 genotype [4]. These PHC patients were AFP- and HBsAg-seropositive, whereas another PHC group had HLA B15 and were AFP-negative. The different gene composition in these PHC patients may indicate that different host phenotypes may respond to environmental carcinogenic stimuli uniquely. The overall presumption that 'ethnic Chinese' are more vulnerable to PHC is supported by the collected data from both Asian Pacific countries [2] and migrant studies [35].

Other important environmental causes include the contamination of water supplies by oncogenic agents (be they viruses that can survive in effluent water or mycotoxins that are heat-resistant). The findings of a higher incidence of PHC in areas where water derived from river beds is used, in contrast to a lower incidence in populations using water from mountain streams, are thus of serious importance [32].

Sex Differences

Epidemiological studies of the Singapore Chinese population (including those of family members of PHC patients) have shown that the male is more vulnerable than his female sibling, who may possess the same genotype B5 and also be HBsAg-positive. These women do not develop PHC even though their brothers develop the disease at a far earlier age than is usual (20–35 years vs 60–70 years). In all series reported [35] in which environmental and genetic factors have been similar, PHC has been more prevalent in males than in females. The male : female ratio in age-standardized incidence rates ranges from 2 : 1 to 4 : 1. The age distribution rises with each decade and reaches a peak in the 6th and 7th decades (32%), the disease being infrequently reported in women under 40 years [24; Singapore Cancer Registry data courtesy of Prof. K. Shanmugaratnam]. Three younger women (25–29 years old) with PHC have recently been described, who had been taking estrogen- and progestogen-containing oral contraceptives for various periods ranging from 3 months to 10 years [24]. In most African countries the peak incidence for females is in the 4th and 5th decades, and there could be other local factors to account for the presentation of PHC at a younger age.

Hormones and PHC

Although there is ongoing controversy concerning the role of hormonal contraceptives in the pathogenesis of PHC in humans, there is no doubt that in experimental animals various steroid hormones (e.g., testosterone) play an important role in the promotion of tumor development in chemically induced PHC [36]. For instance, orchiectomized male rats or hamsters do not develop PHC unless given testosterone [21]. Similarly, orchiectomized animals do not develop the disease when fed with diethylstilbestrol. However, oophorectomized female or intact male rats develop PHC when given testosterone extracts simultaneously with aminobenzene [10].

In humans, studies of one patient with estrogen-induced adenoma revealed a high titer of ER (M. A. Friedman, unpublished work). Cytoplasmic estradiol receptors (ER) have recently been demonstrated in five adult and one pediatric PHC tumor specimens (M. A. Friedman, unpublished work). The amount of ER in tumor is modest (3.0–10.5 fmol/mg cytosol protein) and insufficient comparisons have been made with surrounding normal-appearing liver to permit general conclusions. Both estrogen and progesterone receptors have also been detected in an estrogen-associated hepatic adenoma [16].

Polypeptide hormones, such as growth hormone and thyroxine, are important in vitro and in vivo stimulants of the normal [3] and the neoplastic liver. The growth of murine hepatomas has been slowed by rendering the animals hypothyroid by thyroidectomy, radioactive iodine, or propylthiouracil [19, 29]. Additionally, glucagon and insulin receptors have been detected in murine hepatoma cell lines and correlated with tumor growth rates [20]. Those tumors with less insulin binding had more rapid growth rates. In humans, increased levels of circu-

lating thyroxine [33] and somatomedin [18] have been described in PHC patients. Somatomedins are peptide hormones normally synthesized by the liver, which have biological actions identical to those of insulin and are not detectable by insulin radioimmunoassay. There is little evidence to suggest that hypoglycemia [17] in PHC is due to hyperinsulinemia, and levels of radioimmunoassayable insulin are low in hypoglycemia or in all stages of advanced PHC (C. J. Oon, unpublished work). On the other hand, the levels of circulating basal growth hormone (RIA) are grossly elevated in patients with advancing PHC, in contrast to those in complete remission (C. J. Oon, unpublished work). Also, insulin, growth hormone, glucagon, and hydrocortisone are known to be hepatotrophic to normal liver tissues [3]. Consequently, the findings in Singapore (J. F. Ren, personal communication), showing that insulin and hydrocortisone promote the culture of hitherto growth-resistant PHC cells, are of much interest. If these findings are confirmed and found to be clinically relevant, then manipulation of hormones that serve as promoting factor(s) in the development of human PHC would not only provide opportunities for endocrine therapeutic intervention but might also provide a partial explanation for the transformation from benign to malignant hepatic disease.

Current Therapy

Conventional modalities of therapy have been generally unsatisfactory. The hope that surgery is the ideal therapy is illusory; it is infrequently attempted and is rarely effective. The inability to detect 'early' disease, the multifocality of the disease, and coexisting liver disease usually frustrate surgical attempts. Thus, it is difficult to imagine that surgery will play an important role in the management of PHC in the forseeable future [7, 11].

Similarly, conventional radiation therapy to the liver has not proven to be of definite value. Therapy with 3,000–4,000 rads has resulted in infrequent palliation and short survival [6]. The principal reason for the lack of effectiveness may well be the aggressive clinical course of PHC. Natural history data from the United States and South Africa indicate that the median survival of PHC patients is 3 months or less for debilitated patients, and less than 6 months for those who are more fit [9].

Similarly, chemotherapy trials have been generally unsatisfactory. Use of fluoropyrimidines, nitrosoureas, and antifols has usually yielded a response rate of less than 10% [9]. Whether given IV, IA, or PO, these agents, singly or in combination, are disappointing. The single most effective drug appears to be adriamycin, which results in response rates of 35%–50% and improved survival when used in appropriate patients [12, 23, 27].

More recently, combinations of chemotherapeutic drugs plus radiation have yielded better response rates. Intra-arterial adriamycin and 5-FU plus 2,100 rads of whole-liver irradiation have resulted in responses in 35%–50% of cases, with more than 75% of patients benefitting subjectively (M. A. Friedman, unpublished work). However, 1- and 2-year survival rates after treatment with these agents are still approximately 20% and 10%, respectively, and there are usually few (less than 5%) 5-year survivors who have been treated with chemotherapy plus radiation therapy.

A newer approach has been offered by Order and co-workers [8], who have utilized an isotopically labeled anti-CEA or anti-ferritin antibody. The use of ^{131}I IgG rabbit antibody represents a unique and innovative therapeutic option. Further experience is needed but an initial case report appears promising.

Although diethylstilbestrol (30 mg/day) and carbimazole (40 mg/day) have been individually given to chemotherapy-unresponsive patients, neither drug has significantly prolonged the median duration of survival [27]. Recently, however, two of five PHC patients had objective responses to oral progestationals (M. A. Friedman, unpublished work), and these may be useful palliative agents. Similarly two of four PHC patients with advanced metastatic PHC have unexpectedly survived 1 year after bilateral orchiectomy. Their tumor tissue had shown an increased and closer clustering of testosterone surface receptor markers (C. J. Oon, unpublished work), which were different from those in normal liver tissues. The estrogen antagonist tamoxifen on its own has not been shown to be effective in inducing regressions, but when combined with adriamycin has extended the median survival of six of twelve advanced PHC patients to more than 8 months. This combination appears to be better than adriamycin or tamoxifen used singly. These studies are small and require longer studies for further confirmation.

The Future

If the association between viral hepatitis and PHC is a causal one, it is possible that preventive methods against hepatitis B infections could reduce the incidence of PHC. Results of prophylactic hepatitis B vaccination raises an interesting question: Could vaccination protect the 5%–10% relatively immu-

nodeficient HBsAg-positive carriers [15, 30], who are the individuals at most risk, from developing PHC? Eradication of the virus from the population could be envisioned through 'herd protection' (as was seen in smallpox vaccination) and may help these susceptible individuals. It is also possible that alteration in the antigenic presentation by the new vaccine may be a means of enhancing an immune response in the hepatitis B-immunodeficient individual. The results of the Taiwan and New York vaccine studies are therefore of epidemiological importance.

Furthermore, advances in therapy are to be expected. Use of radiation therapy (either by conventional source or novel isotopic source) is likely to result in improved palliation. Chemotherapy with currently available agents is unlikely to result in further dramatic benefits, but the search for new effective agents is ongoing. Finally, new approaches with hormonal manipulation should yield clinically meaningful benefit. By modulating either sex steroid or polypeptide hormones direct antitumor effects might be achievable.

Primary hepatocellular cancer is likely to remain a major global public health problem for the next one to two decades, even if an effective vaccine is developed. These, and other, new prospects for therapy should be explored in ongoing clinical trials.

References

1. Beasley P (1978) Human HBsAg-positive hepatoma in prospective HBsAg carriers in Taiwan. In: Vyas GN, Cohen SN, Schmid R (eds) Viral hepatitis. Franklin Institute Press, Philadelphia, p 460
2. Boss LP, Bender TR (1979) Seroepidemiology of hepatitis B in the families and villages of five young Eskimos with primary hepatocellular carcinoma. Proc 30th Alaska Science Conference, Sept 19–21, Fairbanks, Alaska
3. Bucher NL, Patel U, Cohen S (1978) Hormonal factors concerned with liver regeneration. In: Porter R, Whelan J (eds) Hepatotrophic factors. Elsevier, Amsterdam, p 95
4. Chan SH, Simons MJ, Oon CJ (1980) HLA antigen in Chinese patients with hepatocellular carcinomas. J Natl Cancer Inst 65: 21
5. Coady A (1975) The aflatoxin-hepatoma-HBAg story. Br Med J 3: 592
6. Cochrane AMG, Murray-Lyon IM, Brinkley DM, Williams R (1977) Quadruple chemotherapy versus radiotherapy in treatment of primary hepatocellular carcinoma. Cancer 40: 609
7. Davidson AR, Tomlinson S, Calne RY, Williams R (1974) The variable course of primary hepatocellular carcinoma. Br J Surg 61: 349
8. Ettinger DS, Dragon LH, Klein J, Sgagias M, Order SE (1979) Isotopic immunoglobulin in an integrated multimodal treatment program for a primary liver cancer: A case report. Cancer Treat Rep 63: 131
9. Falskon G, Moertel CG, Lavin P, Pretorius FJ, Carbone PP (1978) Chemotherapy studies in primary liver cancer. A prospective randomized trial. Cancer 42: 2149
10. Firminger HI, Reuber MD (1961) Influence of adrenocortical, androgenic, and anabolic hormones on the development of carcinoma and cirrhosis of the liver in AXC rats fed *N*-2-fluorenyldiacetamide. J Natl Cancer Inst 27: 559
11. Foster JH (1970) Survival after liver resection for cancer. Cancer 26: 493
12. Friedman MA, Volberding PA, Cassidy MJ, Resser KJ, Wasserman TH, Phillips TL (1979) Therapy for hepatocellular cancer with intrahepatic arterial adriamycin and 5-fluorouracil combined with whole-liver irradiation: A Northern California Oncology Group Study. Cancer Treat Rep 63: 1885
13. Goh KT (1980) Hepatitis B surveillance in Singapore. Ann Acad Med Singapore 9: 136
14. Higginson J (1970) The epidemiology of primary carcinoma of the liver. Recent Results Cancer Res 26: 38
15. Levo Y, Shouval D, Tur-kaspa R, Wollner S, Penchas S, Zlotnick A, Eliakim M (1981) Immunological evaluation of asymptomatic carriers of hepatitis B virus. Clin Exp Immunol 44: 63
16. Macdonald JS, Lippman ME, Woolley PV, Petrucci PP, Schein PS (1978) Hepatic estrogen and progesterone receptors in an estrogen-associated hepatic neoplasm. Cancer Chemother Pharmacol 1: 135
17. McFadzean AJS, Yeung Tse Tse (1956) Hypoglycemia in primary carcinoma of the liver. Arch Intern Med 98: 720
18. Megyesi K, Kahn CR, Roth J, Gordon P (1974) Hypoglycemia in association with extrapancreatic tumors: Demonstration of elevated NSILA-S by new radioreceptor assay. J Clin Endocrinol Metab 38: 931
19. Mishkin S, Morris HP, Yalovsky MA, Narashima Murthy PV (1979) Inhibition of the growth of Morris hepatoma # 44 in rats after induction of hypothyroidism: Evidence that Morris hepatomas are thyroid-dependent. Gastroenterology 77: 547
20. Mishkin SY, Pollack R, Yalovksy MA, Morris HP, Mishkin S (1981) Inhibition of local and metastatic hepatoma growth and prolongation of survival after induction of hypothyroidism. Cancer Res 41: 3040
21. Morris HP, Firminger HI (1956) Influence of sex and sex hormones on development of hepatomas and other hepatic lesions in strain AXC rats ingesting 2-diacetylaminofluorene. J Natl Cancer Inst 16: 927
22. Nicholson G (1980) Incidence of hepatitis B antigenaemia and positive AFP in New Zealand, Western Samoa and Tonga (A pilot study of Polynesian liver disease). Ann Acad Med Singapore 9: 201
23. Oon CJ (1981) The current status of medical treatment for primary hepatocellular carcinoma (PHC). In: Friedman M, Ogawa M, Kisner D (eds) Diagnosis and treatment of upper gastrointestinal tumors. Excerpta Medica, Amsterdam, p 466
24. Oon CJ, Yo SL, Chan SH (1979) Hepatocellular carcinoma in a patient on oral contraception who had been exposed to hepatitis B virus. Lancet II: 194
25. Oon CJ, Okuda K, Pang R (1980a) Primary hepatocellular carcinoma in the Asian Pacific region. Ann Acad Med Singapore 9: 190
26. Oon CJ, Yo SL, Chio LF, Chan SH (1980b) A pilot study on the screening for primary hepatocellular carcinoma in selected high-risk groups in the population using multiple tumour markers. Ann Acad Med Singapore 9: 240
27. Oon CJ, Ghua EJ, Foong WC, Tan LKA, Yo SL, Chang CH, Ho ST, Seah CS (1980c) Adriamycin in the treatment of resectible and irresectible primary hepatocellular carcinoma. Ann Acad Med Singapore 9: 256
28. Peers FG, Gilman GA, Linsell CA (1976) Dietary aflatoxins and human liver cancer. A study in Swaziland. Int J Cancer 17: 167

29. Pezzino V, Vigneri R, Siperstein MD, Goldfine ID (1979) Insulin and glucagon receptors in Morris hepatomas of varying growth rates. Cancer Res 39: 1443
30. Simons MJ, Yu M, Shanmugaratnam K (1976) Immunodeficiency to hepatitis B viral infection and hepatocellular carcinoma. Liver Cancer. Proc 2nd Asian Cancer Conference, Stamford College Press, Singapore, p 61
31. Su Delong (1979) Drinking water and liver cell cancer. An epidemiologic approach to the etiology of this disease in China. Chin Med J [Engl] 92: 748
32. Szmuness W (1978) Hepatocellular carcinoma and the hepatitis B virus. Evidence for a causal association. Prog Med Virol 24: 40
33. Tan WC, Oon CJ, Cheah JS (1980) Raised serum L-thyroxine levels in patients with hepatocellular carcinoma. Ann Acad Med Singapore 9: 129
34. Tang ZY (1980) Screening and early treatment of primary liver cancer with special reference to the Eastern part of China. Ann Acad Med Singapore 9: 234
35. Tock EP, Shanmugaratnam K (1980) Epidemiology of primary liver cancer in Singapore. Ann Acad Med Singapore 9: 193
36. Toh YC (1973) Physiological and biochemical reviews of sex differences and carcinogenesis with particular reference to the liver. In: Klein G, Weinhouse S (eds) Advances in cancer research, vol 18. Academic Press, New York, p 156
37. Velasco M, González-Cerón M, De La Fuente C, Ruiz A, Donoso S, Katz R (1978) Clinical and pathological study of asymptomatic HBsAg carriers in Chile. Gut 19: 569

Received May 11, 1981/Accepted January 20, 1982