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Hepatocellular carcinoma in central Sydney: a 10 year review of patients seen in a medical oncology department

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Abstract

AIM To report a single Australian oncology unit's experience with the management of patients with hepatocellular carcinoma (HCC), in the context of a literature review of the current management issues.

METHODS Retrospective case record review of 76 patients with diagnosis of HCC referred to the unit between 1984 and 1995.

RESULTS Sixty-three patients had adequate records for analysis. Thirty-six (56%) were migrants with half from Southeast Asia. Twenty-four p atients had a documented viral aetiology. Nine (14%) of 51 patients with pathological confirmation of HCC had normal alpha-fetoprotein levels. Median survival of the 20 patients managed palliatively was 5 weeks compared to 16 weeks for the cohort overall. Surgery in 16 patients rendered all initially disease free with a median survival of 88 weeks. Chemoembolisation induced tumor responses in 5 of the 11 patients so treated. Systemic chemotherapy and tamoxifen treatment caused tumor response in two of 12 and one of 25 respectively.

CONCLUSION Prolonged survival of patients with HCC depends on early detection of small tumors suitable for surgical resection. Other active t reatments are palliative in intent and have limited success. In addition to tumor response and survival duration, the toxicities of therapies and the overall quality of life of patients need to be considered as important outcomes. Viral hepatitis prevention and screening of individuals at risk are strategies that are important for HCC management in communities where the disease is endemic.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cause of death from malignancy in the world and the third most common in men[1]. High risk areas such as Asia and Africa are associated with endemic hepatitis B and C infections. In Australia HCC is still a relatively uncommon cancer as it is in most developed nations. In the state of New South Wales the incidence was 2.6 per 100 000 for males and 1.1 per 100 000 for females from 1985 to 1989. The incidence is significantly higher in male and female migrants from China, Taiwan and Vietnam[2].

We reviewed all cases of HCC that were seen in the Department of Medical Oncology at Royal Prince Alfred Hospital a tertiary centre situated in central Sydney between January 1984 to December 1995. Patient demographics, presenting symptoms, disease stage, prognostic indicators as well as treatment and outcomes were determined.

METHOD

Using the Clinical Reporting System (CRS) database in the Department of Medical Oncology, the names of 76 patients with the diagnosis of HCC were obtained. The departmental files and the medical records were then examined and information collected using a proforma. Parameters collected included sex, age, nationality, clinical and pathological status, presenting symptoms, ECOG (Eastern Cooperative Oncology Group) performance status at time of initial contact, presence or absence of cirrhosis, documentation of possible etiological factors and alpha-fetoprotein (AFP) levels. Tumor response to therapy was recorded using WHO response criteria. Partial response was defined as a greater than 50% reduction in the sum of the products of the longest tumor dimension and its widest perpendicular, in

the absence of new lesions. Where disease was not measurable, changes in AFP level were monitored. Complete response was defined as no tumor evident on imaging plus normalisation of AFP if this was measured. Progressive disease was defined as 25% increase in measurable tumor size or sustained increase in AFP.

Survival time was measured from the date of diagnosis to the date of death determined where possible from the hospital records, contact with local doctors and computer search of the New South Wales Cancer Registry databases.

RESULTS

Seventy-six patients with a diagnosis of HCC were seen in the Department during this period. Of these, sixty-three patients had records that contained sufficient information for analysis.

Demographics

The mean age of the patients was 50 years (range 27 -77) with 43 males and 20 females. Fifty-six percent of the patients were born overseas with over half of these born in Southeast Asia (Table 1).

Clinical characteristics

Of 57 patients where data on symptoms were available, thirteen (23%) patients were asymptomatic at the time of diagnosis. Three had an ECOG performance status of 4 (totally bedbound) and six a score of 3 (spending more than 50% of waking hours in bed). The most common presenting symptom was pain in 33 (58%) followed by weight loss in 27 (47%) and abdominal distension in 17 (30%). Sixteen (28%) patients presented with jaundice. The median duration of symptoms before presentation was two months, ranging from immediately prior to presentation up to 50 weeks.

The most common documented aetiological factor for hepatocellular carcinoma in this series was hepatitis B infection in 21 (33%) patients. Five patients had hepatitis C infection, and three of these were co-infected with both hepatitis B and C. Routine testing for hepatitis C at Royal Prince Alfred Hospital only be came available from mid 1989 and retrospective testing was not done in the cohort, which may explain the relatively low infection rate in this series. Five (22%) of the 23 patients with viral hepatitis were Australian born. Of the three patients who had cirrhosis secondary to hemochromatosis all had alcohol as a cofactor. Alcohol was a cofactor in 5 (19%) of the 26 Australian born patients and five (14%) of the overseas born patients. Twenty-three patients had no apparent causative factor. One patient had a past history of low grade lymphoma and another hydatid liver disease. These causative factors are listed in Table 2.

Pathological confirmation of diagnosis was obtained in 51 patients (81%) mainly by fine needle aspiration biopsy. In the remainder, a clinical diagnosis was based on radiological appearance on CT scan or hepatic angiogram and a raised serum AFP level. There were nine patients (14%) with pathological confirmation of HCC who had normal AFP levels at presentation. The initial levels ranged from 0 to 36000 IU. Thirty-five (69%) of the 51 patients where information was available had clinical, pathological or radiological evidence of cirrhosis at initial presentation. Thirty-four patients (of 56 evaluable) had multifocal tumors on imaging or pathology and six had regional node enlargement. Ten of 61 patients (16%) had distant metastases with the sites being lung in (7) and bone (4).

Treatment

Twenty (30%) patients received no anti-tumor treatment and were managed with supportive care. Six of these patients presented with ECOG performance status 3 or 4. The median survival of this group was five weeks from the time of diagnosis.

The remaining 43 patients received some form of anti-tumor therapy. The median time from diagnosis to initiation of treatment was 15 days (range 0 days to 5.2 years). Seventeen patients received two types of therapy and four patients received three or four different treatments.

Surgery was performed in 16 (25%) patients, either in the form of a lobectomy or hemihepatectomy. Three of these patients had surgery after chemoembolization. Two patients had repeat resections for relapse 5 and 39 months after curative resection. No patients in the series received allograft transplantation as their first therapeutic intervention. All patients who underwent surgery were rendered clinically disease free afterwards. Their median survival was 88 weeks (range 5- 354 weeks) from diagnosis or surgery with the median time to relapse being 43 weeks (range 4-182). Two patients are still alive at one year and two years after surgery.

Chemoembolization of the HCC by the selective injection of cisplatin and Lipiodol into the hepatic artery was carried out in 11 (17%) patients. In three patients this was done prior to surgery in an attempt to reduce the vascularity and size of the tumor. One of these patients received alcohol injection into the tumor as well and proceeded to an orthotopic liver transplantation. The other two patients had initial marked falls in the AFP to almost within normal range but these had risen to beyond pretreatment levels prior to surgery. Six patients (55%) had a 50% reduction in AFP with the median time to progression being 25 weeks (excluding the transplanted patient from the calculation of the duration of response). Median

survival from chemoembolization was 48.5 weeks.

Twelve (19%) patients were treated with systemic chemotherapy. Three were given anthracycline treatment alone (2 adriamycin, 1 epirubicin), while others received various combinations of cisplatin, adriamycin, 5-fluorouracil (5FU), etoposide and mitomycin C. Two patients received more than one regimen of chemotherapy. Only two patients had objective tumor responses to chemotherapy. Another two had stable disease. The median time to tumor progression was 26 weeks.

Tamoxifen was administered to 25 (40%) patients, with only one showing evidence of AFP response. The time to progression was 44 weeks. Two other patients had stable disease.

Table 3 summarises the response rates, response duration and overall survival of the groups of patients according to the treatments received. The median survival of the group as a whole was 16 weeks with the mean being 50 weeks.

Table 1 Countries of birth of cohort

Country of Birth	No.
Australia	26
Egypt	3
Europe	11
India	1
Pacific Islands	1
Southeast Asia	20
Unknown	1
Total	63

Table 2 Breakdown of established aetiological factors in cohort

Alcohol	10
Chronic autoimmune hepatitis	3
Hepatitis B	21
Hepatitis C	5
Hepatitis B+C	3
Haemochromatosis	3
Unknown	23
Total	63

Table 3 Summary of treatments received for hepatocellular carcinoma

Treatment	Number of patients (%)	Number responding (%)	Median time to progression (weeks)
Observation	20 (30)		
Surgery	16 (25)	16 (100)	43
Chemoembolization	11 (17)	6 (54)	25
Systemic chemotherapy	12 (19)	2 (27)	26
Tamoxifen	25 (40)	1 (4)	44

DISCUSSION

Despite a variety of therapeutic strategies HCC remains a significant cause of cancer death worldwide. The mainstay of treatment is resection of the disease. This is facilitated by early detection of tumors and by liver transplantation when poor hepatic function would otherwise prevent resection. Other treatments, largely directed at palliation such as chemotherapy (±embolization), percutaneous ethanol injection, radiation and hormone therapy are modest in their effects however they may play a role in conjunction with surgery. Equally or more important strategies are prevention of predisposing illnesses (e.g., hepatitis B) or modification of the cirrhotic pre-malignant field defect.

Hepatic resection is generally only feasible in patients with focal lesions and with adequate underlying hepatic function[3]. Because of tumor stage at presentation and the presence of cirrhosis, the proportion of patients suitable for surgery is generally small. The role of orthotopic hepatic transplantation is still controversial. There have been concerns about the perioperative mortality and the frequency of tumor recurrence in the transplanted liver, but transplantation offers some chance of cure of both the tumor and the cirrhosis. A recent series[4] of 48 patients with small tumors (single <5 cm or no more than three <3 cm) and cirrhosis undergoing transplantation, reported overall survival and disease free survival at four years to be 75% and 83% resp ectively. Ninety-four percent of these patients had underlying viral hepatitis.

Percutaneous ethanol injection of these tumors has usually been restricted to non-surgical candidates and one series from Italy has shown encouraging survival figures where ethanol injection was used instead of surgery[5]. This approach may provide a treatment for patients with no access to resection services or those with poor liver reserve, who are not otherwise able to have a liver transplant. Other forms of imaging-directed destruction such as cryotherapy, laser and thermotherapy may have similar potential.

As is the published experience, we found the response rate with systemic chemotherapy low and of short duration. Doxorubicin, remains the most widely used agent but being liver metabolized it may result in unpredictable toxicity in those with hepatic disease. When used as a single agent it generally has a response rate below 20%[6]. Epirubicin, idarubicin and mitoxantrone all have activity comparable to doxorubicin. Single agent activities of other intravenously administered cytotoxics such as cisplatin, 5-fluorouracil, etoposide and mitomycin C are all in the range of 0%-15%[6]. The Eastern Cooperative Oncology Group[7] has evaluated 432 patients in four sequential trials of varying combinations of 5-FU, streptozotocin, semustine, doxorubicin, zinostatin, amsa crine and cisplatin. The median survival of the group as a whole with systemic chemotherapy was 14 weeks with a one-year survival of only 15%. The best median survival of 24 weeks was obtained with the combination of 5-FU and semustine. Al though any

of these agents may cause greater response rates if given intra-arte rially with or without embolization, most reports of trials of chemotherapy, both single agent and combinations have small patient numbers and none shows a convincing superiority to be considered standard treatment[7,8].

Chemoembolization consists of a relatively selective embolization of the tumor blood supply with agents such as cisplatin and Lipiodol. While theoretically attractive, the technique may result in hepatic decompensation because the cirrhotic liver is more dependent on blood from the hepatic artery than the portalvein. For this reason embolization techniques are suitable for a small group of patients. In the Group D'Etudeetde Traitment du Carcinome Hepatocellularie[9] randomised trial of chemoembolisation versus conservative management in 96 selected patients from 24 centres, there was no significant survival difference detected after accounting for differences in baseline and prognostic characteris tics. Small survival differences however would not be detected by a study of this size. Half of the patients in the treatment group had reduction in AFP levels. These observations are in keeping with the findings in our study. Hepatic decom pensation however was seen in 70% of patients having chemoembolization. Another multicentre randomised study[10] of Lipiodol/ cisplatin chemoembolization in 73 patients also reported no survival difference. Transarterial embolization without chemotherapy in a single institutional study has also demonstrated no survival advantage versus supportive care[11]. In these circumstances, a more appropriate endpoint may be symptom control, analgesic requirements and quality of life rather than survival. Symptomatic rather than asymptomatic patients may be more appropriate candidates for chemotherapy.

Oestrogen receptors have been detected in normal liver tissue and in HCC with the levels tending to be higher in the neoplastic tissue. This provides the rationale of using the anti-oestrogen tamoxifen. Seven randomized trials of tamoxifen versus placebo in advanced HCC have been reported[12-18]. Three[12-14] which had under 38 patients each reported improved survival in the tamoxifen treatedarms. An additional two randomized trials investigating chemo therapy and tamoxifen found no improvement in response or survival when tamoxifen was added to doxorubicin[19] or intra-arterial cisplatin and 5FU[15]. An overview of the published randomised trials of tamoxifen versus active or no active treatment in HCC between 1978 and 1995 suggested a moderate benefit with a 2.2 odds ratio for 1 year survival[20]. However the largest randomized study so far involving 496 patients has recently been presented and showed no survival benefit of tamoxifen compared to supportive care[19].

Antiandrogen therapy has also been tried in HCC on the basis that it is a male predominant disease, it can be induced by androgen therapy and that the receptors are expressed in high levels in the tumors. A European Organisation for Research and Treatment of Cancer (EORTC) multicentre trial[21] compared antiandrogen therapy with a luteinising hormone-releasing hormone (LHRH)agonist either goserelin or triptoreline, with a pure antiandrogen nilutamide alone or in combination against placebo in 244 patients with advanced HCC. No significant difference however was found in any of the groups.

A recent study reports an apparent reduction in the incidence of new primary HCCs in patients administered polyprenoic acid, an acyclic retinoid, after resection for HCC. This strategy targets the pre-malignant field defect that leads to HCC[22].

Radiation therapy has been more usually applied in the form of radioactive ligands injected into the hepatic artery than as external radiation. A preliminary report of a randomized trial from Hong Kong has shown that ^{131}I labelled lipiodol injected post-resection improves the time to tumor recurrence[23]. Similarly data from pilot studies suggest post-transplant/resection - chemotherapy may improve outcome, although randomized trials are still underway[24].

Viral hepatitis is a significant causative factor for HCC in our cohort especially in those born overseas, being present in over one-third. In the migrant population high hepatitis B endemicity accounts for the high prevalence rate. In hepatitis B associated cirrhosis the cumulative incidence of hepatocellular carcino ma has been found to be 59% over a six-year period[25]. With hepatitis C associated cirrhosis, a Japanese prospective study[26] has reported th at 75% of patients will develop HCC by 15 years. Preventative measures such as hepatitis B vaccination in endemic disease populations is obviously an important and effective strategy. A recent study from Taiwan has reported that a national hepatitis B vaccination program has reduced the annual HCC incidence in children of aged 6-14 years from 0.7 to 0.36 per 100 000 ($P< 0.01$), with a similar effect on population mortality[27]. Treatment of viral related chronic active hepatitis with interferon alpha may not only prevent development of cirrhosis but also reduce the frequency of subsequent HCC[28].

Alcohol was also an important risk factor in the Australian born patients in our series. In a larger published series of HCC[29] from western Sydney it was found to be an association in 46% of the Australian patients and only 13% of those born overseas.

Screening of high risk populations for HCC by a combination of serum AFP determination and

imaging with high resolution real time ultrasound can detect HCC at an early stage which might be amenable to curative resection. AFP however can be normal in patients with asymptomatic small tumors. The reliability of ultrasound is operator dependent and many studies have been in Japanese patients who have generally a thinner body habitus which may make imaging easier than in Westerners. Studies suggest that treatment of these early lesions may produce a true survival benefit although there have been no randomized trials reporting mortality reduction from screening[30]. This strategy can only be considered an option in high risk populations, rather than on a general population basis.

CONCLUSION

Hepatocellular carcinoma is becoming a greater problem in developed countries such as Australia with the wave of immigration from countries affected by endemic viral hepatitis. Treatment modalities are unsatisfactory once the tumor has spread and become inoperable. Public health measures need to focus on the targeting of risk factors and surveillance of at risk subgroups.

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