Patterns of presentation, referral, and treatment of hepatocellular carcinoma in a pre-sorafenib era: experience of a Canadian provincial cancer agency

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ABSTRACT

Background

Systemic treatment options in hepatocellular carcinoma (HCC) are limited. Sorafenib, a multikinase inhibitor, has been shown to improve survival in patients with advanced HCC and adequate hepatic reserve. Currently, the proportion of referred patients with HCC that would be eligible for sorafenib therapy is unclear. We reviewed patterns in the presentation and management of referred patients with HCC at the BC Cancer Agency (BCCA) before the availability of sorafenib.

Methods

Records of patients with HCC referred to the BCCA from January 1, 2003, to December 31, 2007, were reviewed. Distributions were analyzed using frequency statistics.

Results

Of 518 patients reviewed, 77% were men and 45% were of Asian ethnicity; median age was 64 years. Histology confirmation was available in only 34% of the patients; 64% had an elevated level of alpha-fetoprotein at diagnosis. The Child–Pugh score at presentation could not be determined in 56%; the most common missing variable was albumin (44%). Among the 226 evaluable patients, the Child–Pugh classification was A in 140 (62%), B in 64 (28%), and C in 22 (10%). Eastern Cooperative Oncology Group performance status was not documented in 40% of patients. The TNM staging was recorded per agency protocol; however, it was incompletely documented in most patients. Distant metastases were recorded in 12% of patients, and 75 patients (15%) underwent hepatic resection before referral. After BCCA referral, no further therapy was offered to 287 patients (54%), regional therapy was offered to 170 (33%), and chemotherapy was offered to 67 (13%).

Conclusions

In this era of targeted therapies, characterizing the proportion of patients with HCC that would be eligible for such therapies is important. In our experience, referred patients are commonly Asian men with an acceptable hepatic reserve by Child–Pugh score, who have been diagnosed by clinical criteria alone. Most patients were offered no further therapy. Moving forward, accurate and systematic documentation of staging, performance status, and Child–Pugh score per the Barcelona Clinic Liver Cancer staging protocol will be imperative to best identify patients who may benefit most from sorafenib or available clinical trials, and to subsequently evaluate the population-based impact of the introduction of such therapies in patients with advanced HCC.

KEY WORDS

Sorafenib, HCC, targeted therapy

1. INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is on the rise, with an estimated 711,000 new cases diagnosed worldwide during 2007 alone [1]. Furthermore, the incidence of HCC is virtually identical to the number of deaths annually, emphasizing the high lethality of the disease. That lethality is a reflection of the fact that HCC is often diagnosed at an advanced stage, when treatment options are limited.

For many reasons, systemic therapy has not routinely been used for people with advanced HCC. Patients often have significant underlying hepatic dysfunction, limiting the tolerability of chemotherapy because of hepatotoxicity and impaired marrow reserve. Until recently, doxorubicin has been the most-studied chemotherapy agent for advanced HCC, with a few early trials suggesting that, compared with best supportive care alone, it provides a small survival advantage [2]. However, subsequent

studies failed to confirm the initial positive reports on doxorubicin or any other single agent. In fact, the prevailing consensus is that no single agent (or combination of agents) given systemically has had a significant effect on survival [3].

Molecularly targeted therapy is a new paradigm in oncology. Targeted agents act by interfering with pathways critical for cancer survival, including tumour angiogenesis and growth-signalling cascades. Sorafenib (Nexavar: Bayer HealthCare AG, Leverkusen, Germany) is one such agent. It acts by inhibiting the Raf/Mek/Erk pathway, and it also targets angiogenesis [4,5]. In the phase III randomized double-blind placebo-controlled Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, conducted to assess the efficacy and safety of sorafenib in patients with advanced HCC [6], 602 patients with a Child–Pugh score of A (and some B scores) who had not received previous systemic treatment were randomized to receive either sorafenib or placebo. Treatment continued until both radiologic (defined by the Response Evaluation Criteria in Solid Tumors [7]) and symptomatic progression occurred or until either an unacceptable adverse event or death occurred. Results of this landmark study showed that overall survival was significantly longer in the sorafenib group than in the placebo group (10.7 months vs. 7.9 months).

To understand the generalizability of the findings from this pivotal multinational clinical trial to a real-world setting, a better understanding of the characteristics of patients diagnosed with HCC in the region of interest is imperative. The proportion of people with HCC that would be eligible for first-line treatment with sorafenib is unclear. The purpose of the present study was to gain a better understanding of the demographics and referral patterns of patients pre-sorafenib so that those patterns can be followed prospectively to see if the availability of a proven systemic therapy (that is, sorafenib) truly affects patterns of practice beyond treatment—for example, referral patterns and demographics. Our review also serves as the foundation for a prospective provincial HCC registry and outcomes database.

2. METHODS

2.1 Data Sources

Records of patients with HCC referred to the BCCA from January 1, 2003, to December 31, 2007, were retrospectively reviewed by a single observer. The dates chosen reflect the population in the pre-sorafenib era, before the results of the SHARP trial were reported. The review covered 518 cases. After ethics approval was obtained, data were collected (using an established data collection form and a newly created data dictionary) from charts found in the electronic Cancer Agency Information System under the HCC code. The data abstracted included demographics (BCCA identification number, sex, date of birth, ethnicity), referral information (source, centre, date of diagnosis), clinical information [method of diagnosis, risk factor and hepatitis status, Child–Pugh score, Eastern Cooperative Oncology Group (ECOG) performance status, alpha-fetoprotein (AFP), stage at presentation], treatment information (treatment received before referral, first- and second-line treatments), and date and status at last follow-up. Data were abstracted from various source documents, including referral letters, initial consultation notes, and results of imaging and laboratory investigations.

2.2 Statistical Analysis

Distributions were analyzed using frequency statistics, and survival was analyzed using the Kaplan–Meier method.

3. RESULTS

Table I presents the demographics of the study patients. Most were men (77%), and 44% were of Asian ethnicity. The median age at diagnosis was 64 years (range: 22–92 years); average age was 63 years.

Table II reviews the risk factors for HCC as documented for the patient cohort. The most commonly identified factors were cirrhosis (48%), hepatitis B (29%), and hepatitis C (20%); however, hepatitis status was unavailable by history or documentation of serology in most cases. Similarly, alcohol consumption was not recorded in most patient records (86%). As risk factors for HCC, α1-antitrypsin, hemochromatosis, and Wilson disease were extremely rare in this population (<1% having any one of those risk factors).

Most patients referred to the BCCA for assessment came from either the Greater Vancouver area (73%) or Victoria (10%). Furthermore, 90% were new patients referred shortly after a diagnosis of HCC, compared with 10% who were referred with active disease after

TABLE I Patient demographics

Variable	*Value* (n)	*Value* (%)
Sex		
Male	400	77.2
Female	118	22.8
Ethnicity		
Asian (all)	231	44.6
Non-Asian	287	55.4
Age at diagnosis (years)		
Median	64	
Mean	63	
Range	22–92	

TABLE II Risk factors for hepatocellular carcinoma

Factor	Patients (n)	Patients (%)
Hepatitis B		
Yes	152	29.3
No	100	19.3
Not recorded	266	51.4
Hepatitis C		
Yes	102	19.7
No	102	19.7
Not recorded	314	60.6
Alcohol		
Yes	42	8.1
No	33	6.4
Not recorded	443	85.5
Cirrhosis		
Yes	248	47.9
No	37	7.1
Not recorded	233	45.0
Other[a] (*n*=2072)		
Yes	13	0.6
No	2038	98.4
Not recorded	21	1.0

[a] α1-Antitrypsin, hemochromatosis, Wilson disease, cryptogenic.

a period of remission that initially had been treated elsewhere. Of the patients that had experienced a period of remission, most had received locoregional treatments; only 2 had received systemic treatment with doxorubicin. Referrals to the BCCA most commonly came from general surgeons (39%), family physicians (24%), gastroenterologists (16%), and general internists (13%).

The diagnosis of HCC was most commonly made using clinical and imaging criteria alone (47%); diagnoses by pathology specimen (34%) and cytology (19%) were next. In patients with pathology or cytology diagnoses, the most common histology was "HCC not otherwise specified" (95%), followed by trabecular (1%) and clear-cell histology (1%).

Functional reserve of the liver was assessed using the Child–Pugh score [3], and patient reserve was assessed using ECOG performance status. The 5-parameter Child–Pugh score was calculated for all patients using the first laboratory values recorded in the Cancer Agency Information System at the time of referral; ECOG performance status was abstracted from consultation notes (Table III). In cases in which the Child–Pugh score was able to be calculated, most patients were scored A (62%) or B (28%). The ECOG performance status was not specified in many cases (40%); however, when performance status was documented, most patients had a performance status of 0 (45%).

Almost two thirds (64%) of the patients had an abnormal AFP value (>11 ng/mL); in 21%, the value was normal, and in 15%, no value had been recorded. The median AFP was 111 IU/L (range: 1.6–13,000,000 IU/L).

Table IV presents the TNM staging in the patients. When information was recorded and complete, most patients had T0–2 disease (36%). Confirmed distant metastases were present in only 12% of patients. The presence or absence of metastases was usually determined based on imaging rather than on pathology.

Table V presents treatment information, including treatment received before referral and that received subsequently. Before referral, most patients (75%) received no treatment of any type. If they did receive treatment before referral, that treatment most likely came in the form of regional therapy (28%), with resection (15%) being the most common type of regional treatment. Two patients received doxorubicin. Nineteen patients received a combination

TABLE III Measures of functional reserve

Variable	Patients (n)	Patients (%)
Child–Pugh score		
A	140	27.0
B	64	12.4
C	22	4.2
Not recorded	292	56.4
ECOG performance status		
0	140	27.0
1–2	105	20.3
3–4	68	13.1
Not recorded	205	39.6

ECOG = Eastern Cooperative Oncology Group.

TABLE IV Staging information

Stage	Patients (n)	Patients (%)
T		
x	159	30.7
0–2	189	36.5
3–4	170	32.8
N		
x	253	48.9
0	243	46.9
1	22	4.2
M		
x	210	40.5
0	244	47.1
1	64	12.4

TABLE V Treatment information

Treatment	Patients (n)	Patients [% overall (% of subgroup)]
Before referral		
Regional	144	27.8
Resection	75	14.5 (52.1)
Ablation	34	6.6 (23.6)
Chemoembolization	35	6.8 (24.3)
Systemic	2	0.4
None	390	75.3
Two of the above	18	3.5
First-line (that is, first after referral)		
Regional	170	32.8
Resection	28	5.4 (16.5)
Ablation	11	2.1 (6.5)
Chemoembolization	131	25.3 (77.1)
Systemic	67	12.9
Sorafenib	10	1.9 (14.9)
None	287	55.4
Other	1	0.2
Two of the above	8	1.5
Second-line (that is, second after referral)		
Regional	24	4.6
Resection	4	0.8 (16.7)
Ablation	4	0.8 (16.7)
Chemoembolization	14	2.9 (62.5)
Systemic	38	7.3
Sorafenib	12	2.3 (31.6)
None	457	88.2

of two types of treatment. In the cases in which the patient received two types of treatment, two forms of regional therapy were typically involved: usually resection followed by ablation.

After referral, most patients received no further therapy (55%). Among the patients offered first-line treatment, the most common intervention was chemoembolization (25%). Systemic therapy was administered in 67 patients (13%). The systemic treatments given ranged from doxorubicin to various combination treatments. Only 12% of patients received any form of second-line treatment, with most receiving chemotherapy (7%).

As illustrated by the Kaplan–Meier plot (Figure 1), the observed median survival, regardless of stage of disease, was 12.5 months in all patients, with a 5-year survival rate of 17%.

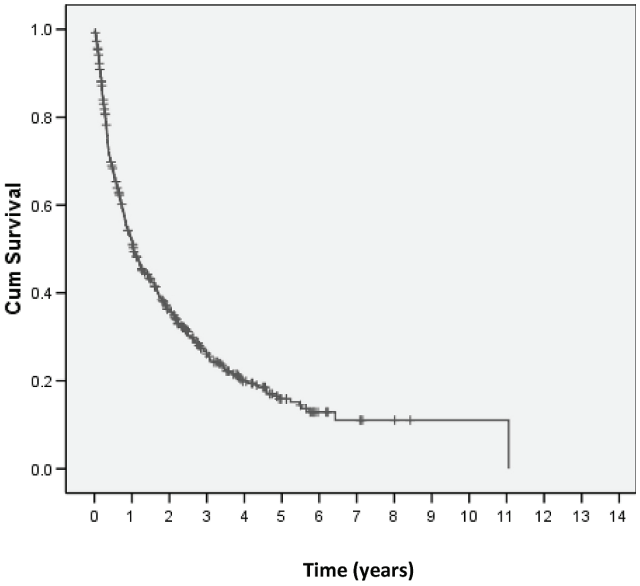

FIGURE 1 *Kaplan–Meier outcome data of overall survival against time (years).*

4. DISCUSSION

Patients with HCC referred to the BCCA are typically men with an average age of 63 years. This preponderance of men is already known and is even more pronounced in high-incidence regions, presumably because of sex-related variations in hepatitis carrier states, exposure to environmental toxins, and the trophic effects of androgens [8]. With respect to age, HCC tends to occur in older individuals who have had time to accumulate risk factors for the disease. Several large prospective studies conducted in Asia and Western Europe noted a mean age at presentation of between 50 and 60 years [9–11]. Similarly, a population-based study in the United States noted that the incidence of HCC was highest among Asians—again, likely related to the underlying causes of liver disease and genetic and environmental factors [12].

There are many known risk factors for HCC. Patients with chronic liver disease or cirrhosis have a very high risk for developing HCC. The most common causes of cirrhosis in the Western world are hepatitis and chronic alcohol use [13]. In our cohort, the dominant causes in the patients with documented hepatic cirrhosis were alcohol, hepatitis B, and hepatitis C. It is noteworthy that, although hepatitis C is the most common viral hepatitis in the Western world, hepatitis B was more common in our study cohort. That finding is likely a reflection of the relatively higher proportion of patients of Asian ethnicity [14]. According to the 2006 census, 26.1% of the B.C. population is made up of individuals from East and Southeast Asia, constituting the largest ethnic population in British Columbia [15].

Treatment decisions in HCC are, as in other solid tumours, largely driven by disease stage and end-organ reserve. The TNM staging system is of limited utility in HCC because it is based on pathology findings in specimens usually obtained at the time of surgery, and as previously mentioned, surgery is appropriate in only a small percentage of the population with HCC. A few staging systems for HCC have been developed, including the Barcelona Clinic Liver Cancer (BCLC) staging system (Figure 2) and the Japan integrated staging (JIS) system. The JIS score is best for patients diagnosed at an early stage and treated with radical therapies such as resection [16]. As previously stated, those patients are not in the majority. In addition, the JIS is more useful for prognostication than for guiding treatment. On the other hand, the BCLC staging system uses several variables, including tumour stage, liver function status, and physical status to actually help guide treatment.

In the present review, as Table IV illustrates, staging information was not readily available in many cases because either the primary tumour, the nodal status, or the sites of distant metastases could not be assessed. Furthermore, Table III shows that in 56% of cases, the Child–Pugh score was unknown either because it was not clearly documented or could not be determined because of missing data (usually serum albumin). Similarly, ECOG performance status was not recorded in almost 40% of the charts reviewed.

Currently, the BCCA utilizes TNM staging, which does not take into account the extent of underlying liver disease. By contrast, the BCLC staging system is a more treatment-driven approach that would require systematic documentation of Child–Pugh score and ECOG performance status for its application. As greater opportunities arise for systemic therapies in HCC, it is important that these gaps in assessment be recognized.

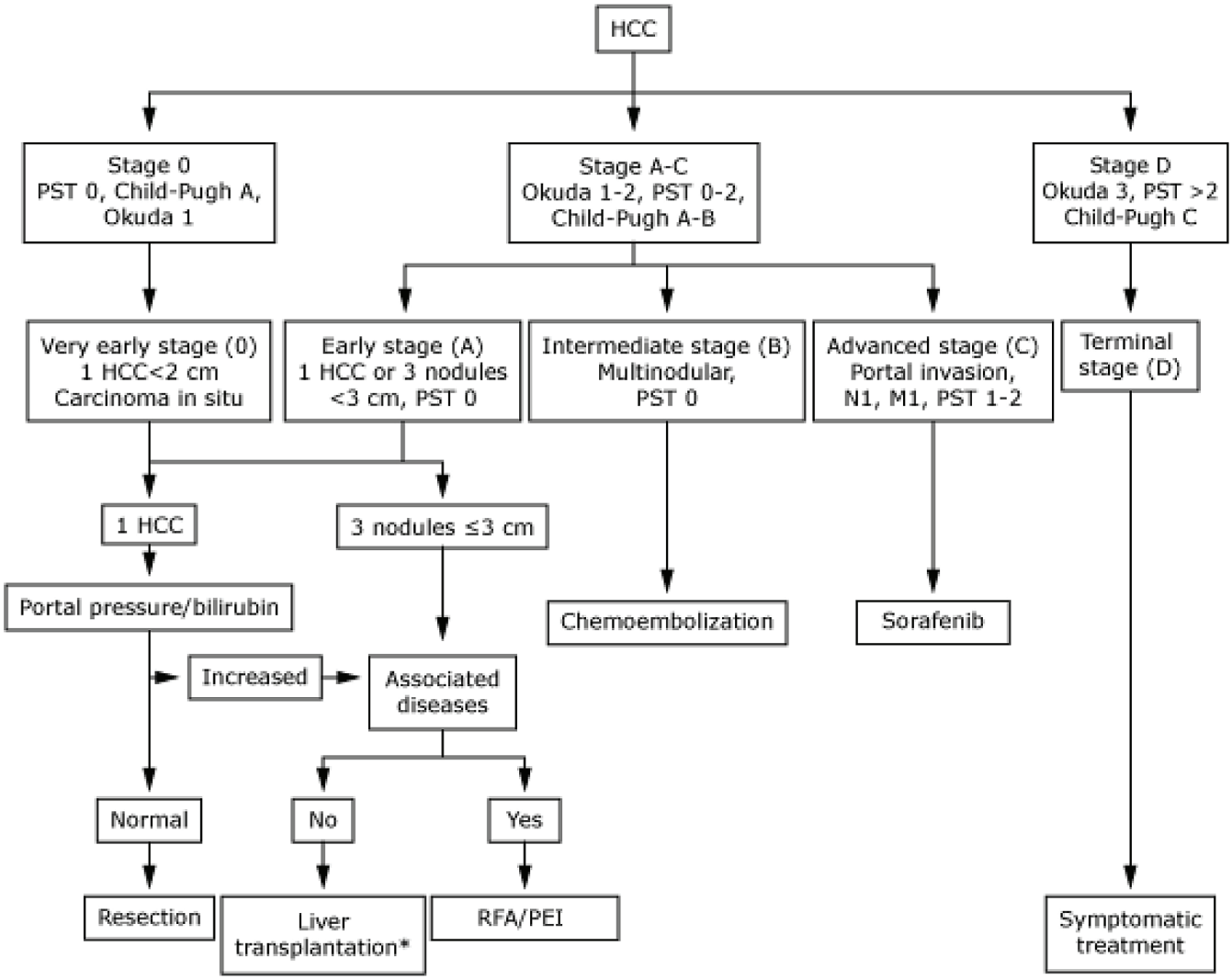

*FIGURE 2 Barcelona Clinic Liver Cancer staging system and treatment options [18]. HCC = hepatocellular carcinoma; PST = performance status; RFA = radiofrequency ablation; PEI = percutaneous ethanol ablation. * Cadaveric or from a living donor.*

In this pre-sorafenib cohort, more than half the referred patients were not offered any form of treatment. When treatment was offered, the intervention typically suggested was transarterial chemoembolization. First-line systemic treatment, primarily intravenous doxorubicin, was offered to 67 patients (13%).

Despite the limitations of the present review, it might be speculated that the patients who were not offered systemic treatment might have benefited from sorafenib and might have been able to tolerate it well and thus accrue its benefits. As previously mentioned, the SHARP study showed that median survival was approximately 7.9 months in the group that received no treatment. Figure 1 shows that the median survival of patients with HCC in our cohort was 12.5 months. However, it is important to note that stage of disease is not taken into account in that analysis. Because staging information was missing in most of the patients studied, the curve reflects survival in a very heterogeneous population with disease at a variety of stages. The curve therefore most likely represents a median survival that perhaps betters the survival reported in the SHARP study.

To generalize the results from the pivotal SHARP trial, a comparison of that study population to our real-world cohort is useful. The demographic profile of the patients in the SHARP trial who were treated with sorafenib is similar to that of our cohort: most were men and the median age was 64 years. In our review, most patients were of Asian ethnicity. In a parallel study published in *The Lancet Oncology,* the efficacy and safety of sorafenib was tested in patients from the Asia–Pacific region with advanced HCC [17]. That study concluded that sorafenib is effective and well tolerated. Integrating that information with the results from the SHARP study, sorafenib would seem to be an appropriate option for our patients with advanced HCC. Most of the patients in our referred cohort met the SHARP entry criteria, having a Child–Pugh score of A and a performance status of 0–2 (when recorded), although we acknowledge that many of the parameters were not recorded. It is therefore difficult to make confident conclusions about the population at large. However, a look at the cases in which information was complete suggests that the patients with HCC being evaluated in clinical practice are comparable to those in the SHARP cohort, and it might be reasonable to generalize the results of that positive study to the BCCA referred population.

5. CONCLUSIONS

Our retrospective review has highlighted many trends in patients with HCC referred to the BCCA. Incomplete recording of baseline factors such as Child–Pugh score and ECOG performance status was a significant limitation, but that incompleteness may reflect the reality that those data were less relevant in an era in which supportive care was the standard for patients not amenable to regional therapy. However, as more treatment options become available, it is important that such gaps be recognized, because these data are useful in a population that may be eligible for novel therapies such as sorafenib and for ongoing clinical trials.

Furthermore, the current TNM staging system is inadequate and not clinically applicable; results from the present study indicate that movement should perhaps begin toward a treatment-driven staging system such as the BCLC staging system. Prospective capture of information such as the Child–Pugh score and the ECOG performance status could be vital when a treatment algorithm such as the BCLC, which is more applicable to clinical practice, is used. A standardized staging form for prospective data collection would capture key baseline characteristics, avoiding such gaps in documentation.

Finally, this review provides a basis and a rationale for starting a prospective provincial HCC registry and outcomes database. Given that sorafenib has become integrated into clinical practice, it would be worthwhile to evaluate temporal trends in outcomes and to compare patients in the pre- and post-sorafenib eras to determine the population-based effects of new therapies on the care and outcomes of patients with HCC in British Columbia.

6. CONFLICT OF INTEREST DISCLOSURES

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