Original Article

Treatment Outcomes with Long Acting Octreotide in Inoperable Hepatocellular Carcinoma: a Local Experience and Review of Literature

Muzaffar Lateef Gill, Muslim Atiq, Syma Sattar, Nasir Khokhar
Department of Gastroenterology, Shifa International Hospital, Islamabad.

Abstract

Objective: To determine the efficacy of long acting octreotide (LAR) in the treatment of inoperable hepatocellular carcinoma; as well as to estimate the improvement in the quality of life.

Methods: This study was carried out at the Shifa International Hospital, Islamabad between February and September 2003. Patients were recruited after an informed consent. There were 22 patients who decided to take the medication whereas 20 patients refused due to socio-economic issues. They served as controls.The patients agreeable for treatment were administered octreotide 100 mcg subcutaneously thrice daily for two weeks. This was followed by monthly administration of 20 mg intramuscular octreotide. The patients were followed up for 6 months. Tumor size, alpha-fetoprotein levels, and improvement in quality of life (QOL) were monitored during therapy.

Results: Out of 22 patients, 19 patients completed the treatment. All were males. Mean age at presentation was 55 years. Tumor size regression was seen in 10 out of 22 patients (45.5%). Mean alpha-fetoprotein levels decreased in 11 out of 22 (50%) patients. An improvement in the quality of life was seen in 10 out of 22 (45.5%) patients after treatment with long acting octreotide. In the treatment arm, 14 out of 22 (64%) patients were alive at the end of six months as compared to 10 out of 20 (50%) in the control group.

Conclusion: LAR causes tumor size regression, decreases AFP levels and improves quality of life in patients with inoperable hepatocellular carcinoma (JPMA 55:135;2005).

Introduction

Hepatocellular carcinoma (HCC) is widely distributed in different geographical areas. There is a high prevalence in Asia and Africa[1] whereas the prevalence is very low in Western societies.[2] In Pakistan its incidence is 8/100,000 per annum[3], Viral hepatitis has been found to account for most of the HCC cases.[4]

Treatment of inoperable HCC remains unsatisfactory and different therapeutic regimes have been tested. Recently trials with tamoxifen[5], flutamide[6] and chemoembolisation with lipiodol[7-10] have been reported.

Somatostatin, a hormone with well proven efficacy for the treatment of hormone producing tumors,[11] has been tested for efficacy in non-hormone producing tumors.

Somatostatin receptors have been identified in various Adenocarcinomas including breast, kidney, large bowel, and ovary.[12,13] Significant decrease in the tumor size and AFP levels were first reported by Kouroumalis and colleagues using long acting octrotide (LAR).[14] Since HCC in Pakistan presents with an advanced stage in a high proportion of patients[15,16], it is important to determine optimal treatment strategy for our patients with HCC. With this background, we decided to determine the efficacy and safety profile of long acting octreotide in advanced stage HCC.

Patients and Methods

This observational study was carried out at the Department of Gastroenterology, Shifa International Hospital, Islamabad. The study was conducted after approval by the institutional review board and hospital ethical committee.

We enrolled 42 patients in the study between February 2003 and September 2003. All patients had a detailed history and physical examination by the consultant gastroenterologist. The diagnosis was made by ultrasound (US) or Computed Tomography (CT) guided biopsy, and measurement of alpha-fetoprotein (AFP). After establishing the diagnosis, the prognosis of the disease was also explained to the patient and family members.

We staged patients using Okuda staging system, which takes into account tumor size, presence of ascites, bilirubin and mean albumin levels. Since we were interested in patients with advanced hepatocellular carcinoma, we included patients only with Okuda stage III.

After establishing the diagnosis and staging the disease extent, the prognosis was explained. These patients were referred to a consultant surgeon for possible resection of the lesion. Only if surgical resection was not possible or considered not to have any possible benefit to the patient, remaining treatment options were discussed with the patient. Out of the 42 patients, 20 refused to undertake the treatment due to financial issues. Therefore we divided the patients into two groups; 22 patients undergoing treatment served as cases whereas 20 who could not afford the treatment served as controls. It was discussed that administering octreotide was only a palliative measure. After obtaining informed consent, the treatment regimen was initiated. First 100µcg of octreotide was administered subcutaneously three times a day for two weeks. Thereafter, 20 mg of LAR was given intramuscularly every month for 6 months.

In order to assess the improvement in QOL measures, Likert scale values between 1-5 were assigned to four variables including pain control, appetite, energy level and over-all well being.

Symptoms were rated as, "excellent" (total resolution), "good" (substantial improvement), "fair" (minor improvement), "poor" (no change) and "very poor" (worse outcome). Tumor size regression was assessed by repeated ultrasound every 2 months whereas decrease in alpha-fetoprotein levels was documented by doing AFP every 3 months. We used a paired t-test to compare the treatment efficacy in this subgroup.

Results

The mean age of the study group was 52.5 years (45-60 years). All patients were males and 15 (68%) under treatment had hepatitis C as a cause of HCC, 5 (23%) hepatitis B and in 2 (9%) patients the cause of HCC was unknown. The treatment was stopped in three because of side effects. Nineteen patients continued the treatment for 6 months.

Since our study was based on multi-focal tumors, we measured the size of the lesion biggest in size; designated as the index tumor. Amongst patients undergoing treatment, mean tumor size at the initial presentation was 5.0±1.0 cm whereas mean AFP levels at the time of initial presentation were 15000±1000 IU/L. However, index tumor size and AFP levels in patients serving, as controls were 4.5± 1.5 and 14500±750 IU/L respectively.

A drop in tumor size greater than 25% was seen in 10 out of 22 (45.5%) patients undergoing treatment. Mean tumor size in these patients was 3.5 cm at the end of treatment. AFP levels decreased in 11 out of 22 (50%) patients

Table 1. Tumor size and AFP levels before and after treatment with LAR in HCC (n=22).

	Before treatment	After treatment (mean score)	p-value
Tumor size (cms)	5.00 ± 1.00	3.0 ± 1.00	0.05
AFP levels (IU/L)	15000 ± 1000	8000 ± 1000	0.04

Table 2. Likert Scale for assessing quality of life pre-treatment and post -treatment (n=22).

	Before treatment (mean score)	After treatment (mean score)	p-value
Pain control	2	4	0.004
Appetite	2	4	0.003
Energy level	2	4	0.003
Overall wellbeing	2	4	0.001

treatment. AFP levels decreased in 11 out of 22 (50%) patients under treatment. In this subgroup, mean AFP levels at the end of treatment, were 8000 IU/L. (Table 1)

QOL indices for pain control, appetite, energy level, and over all well being improved in 10 out of 22 (45.5%) patients from a mean score of 2 to a mean score of 4. (Table 2)

Out of 22 patients, 14 (64%) were alive at the end of the 6 months follow-up whereas 10 out of 20 (50%) patients in the control arm died at the end of follow up for 6 months (Figure).

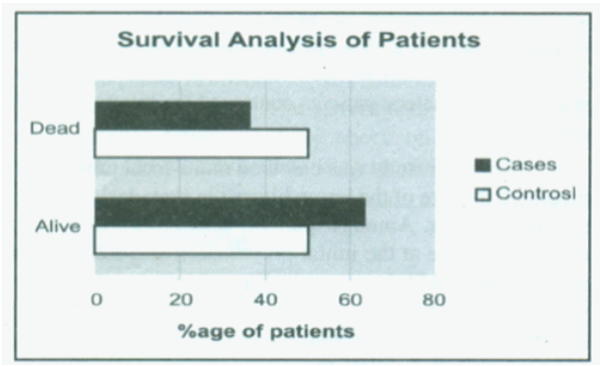

Figure. Survival analysis at the end of 6 months.

No serious side effects were seen in any patients who continued the treatment. However two patients developed diarrhea and discontinued the treatment.

Discussion

The most common etiology for HCC in our patient population was Hepatitis C. This has also been validated by other studies from Pakistan.[15-19]

In our observation, long acting octreotide caused a decrease in the tumor size and decrease in AFP levels at three and six months after treatment amongst patients with inoperable hepatocellular carcinoma.

Since we do not currently have long term follow up of these patients, it is not possible to determine the efficacy of the regimen in terms of increasing median survival. However, it is important to take into account the fact that 64% patients were alive at the end of 6 months of treatment where the median survival for patients with advanced disease has been reported between 2 to 4 months in untreated patients.[14,18,20,21]

The improvement in quality of life was considered an important variable to be assessed in the study population. The Likert Scale was used to assess the quality of life in patients undergoing treatment. Around 45% of the patients showed an improvement in the quality of life index.

There have been conflicting reports about the efficacy of long acting octreotide in hepatocellular carcinoma. In a cohort of 63 patients from Germany, a partial remission in tumor size was achieved in only two patients (3.17%) after three months of treatment but without any difference in median survival of these patients.[20] Likewise, investigators from Hong Kong found no differences in the cumulative survival, tumor size regression, drop in AFP and quality of life between the LAR treated and untreated groups.[21]

On the contrary, Greek investigators have shown a significant difference in the median survival time and a substantial improvement in the quality of life. However, no reduction in the AFP levels or a decrease in the tumor mass was observed.[22]

In one study from Pakistan, high dose octreotide was shown to cause a significant decrease in AFP levels and improvement in the quality of life of the treated patients.[23]

Although we do not have enough evidence if LAR increases the long-term survival of patients with HCC, the significant improvement in the quality of life is an important variable to be taken into consideration. This certainly refers to the palliative care measures in terminally ill patients.

Limitations

Some of the pertinent limitations of the study include being a non-randomized trial. Also the lack of long-term follow up at this stage and the fact that this study was based at a single center are other factors to be considered.

Conclusion

Long acting octreotide improves quality of life and tumor regression in a high proportion of patients. However, multi-center, controlled, randomized trials with adequate follow up are needed to accept or refute this idea.

References

1. Scudamore CH, Ragaz J, Kluftinger AM, Owen DA. Hepatocellular carcinoma: a comparison of oriental and Caucasian patients. Am J Surg 1988;155:659-62.
2. Wong F, Choi TK. Primary liver cell cancer. Asian experience. In: Blumgart LH (ed). Surgery of liver and biliary tract. London: Churchill Livingstone, 1988, pp.1135-51.
3. Mujeeb SA, Jamal Q, Khanani R, Iqbal N, Kaher S. Prevalence of hepatitis B surface antigen and HCV antibodies in hepatocellular carcinoma cases in Karachi, Pakistan. Trop Doct 1997;27:45-6.
4. Qureshi H, Zuberi SJ, Jafarey NA, Zaidi SH. Hepatocellular carcinoma in Karachi. J Gastroenterol Hepatol 1990;5:1-6.
5. Tong CY, Khan R, Beeching NJ, Tariq WU, Hart CA, Ahmad N, et al. The occurrence of hepatitis B and C viruses in Pakistani patients with chronic liver disease and hepatocellular carcinoma. Epidemiol Infect 1996;117:327-32.
6. Mannesis EK, Giannoulis G, Zoumpoulis P, Vafiadou I, Hadjiyannis SG. Treatment of hepatocellular carcinoma with combined suppression and inhibition of sex hormones: a randomized, controlled trial. Hepatology 1995;21:1535-42.
7. Chao Y, Chan WK, Huang YS, Teng HC, Wang SS. Phase II of flutamide in the treatment of hepatocellular carcinoma. Cancer 1996;77:635-9
8. Ram AM, Bhattacharya S, Novell JR, Dick R, Winslet MC, Hobbs KEF. Intra-

8. Ram AM, Bhattacharya S, Novell JR, Dick R, Winslet MC, Hobbs KEF. Intra-arterial radiotherapy with 131 iodine-lipiodol for irresectable hepatocellular carcinoma(abstract). Gut 1996;38 (suppl 1):A17.
9. Madden MV, Krige JEJ, Bailey S, Beningfield SJ, Geddes C, Werner FD, et al. Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 1993;34:1598-1600.
10. Rossi P, Rossi M, Clementi M, Pizzamiglio M, Bezzi M, Salvatori FM. Chemoembolization of hepatocellular carcinomas. Proceedings, European seminars on diagnostic and interventional radiology. Heraklion: 1994, pp. 315-20.
11. Bhattacharya S, Novell JR, Dusheiko GM, Hilson AJ, Dick R, Hobbs KE. Epirubicin-lipiodol chemotherapy versus 131 iodine-lipiodol radiotherapy in the treatment of unresectable hepatocellular carcinoma. Cancer 1995;76:2202-10.
12. Lamberts SWJ, Van Der Lely AJ, de Herder WW, Hofland LJ. Octreotide. N Engl J Med 1996;334:246-54.
13. Reubi JC, Kvols L, Krenning E, Lamberts SWJ. Distribution of somatostatin receptors in normal and tumour tissue. Metabolism 1990;39(Suppl 2):78-81.
14. Lamberts SWJ, Krenning EP, Reubi JC. The role of somatostatin and its analogues in the diagnosis and treatment of tumours. Endocr Rev 1991;12:450-82.
15. Kouroumalis E, Skordilis P, Thermos K, Vasilaki A, Moschandrea J, Manousos ON. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. Gut 1998;42:442-7.
16. Khokhar N, Aijazi I, Gill ML. Spectrum of hepatocellular carcinoma at Shifa International Hospital, Islamabad. J Ayub Med Coll 2003;15:1-4.
17. Rehman AU, Murad S. Hepatocellular carcinoma: a retrospective analysis of 118 cases. J Coll Phys Surg Pak 2002;12:108-9.
18. Butt A, Khan A, Alam A, Ahmad S, Shah S, Shafqat F, et al. Hepatocellular carcinoma: analysis of 76 cases. J Pak Med Assoc 1998;48:197-201.
19. Shah HA, Jafri W, Malik I, Prescott L, Simmonds P. Hepatitis C virus (HCV) genotypes in Pakistan. J Gastroentrol Hepatol 1997;12:758-61.
20. Sharieff S, Burney I, Salam A, Siddiqui T. Hepatocellular carcinoma. J Coll Phys Surg Pak 2002;12:264-7.
21. Rabe C, Pilz T, Allgaier HP, Halm U, Strasser C, Wettstein M, et al. Clinical outcome of a cohort of 63 patients with hepatocellular carcinoma treated with octreotide. Z Gastroenterol. 2002;40:395-400.
22. Yuen MF, Poon RTP, Lai CL, Fan ST, Lo CM, Wong KW, et al. A randomized placebo-controlled study of long acting octreotide for the treatment of advanced hepatocellular carcinoma. Hepatology 2002 36:687-91.
23. Farooqi JI, Farooqi RJ. Efficacy of octreotide in cases of inoperable hepatocellular carcinoma: a clinical trial. J Coll Phys Surg Pak 2000;10:258-60.