Chemoradiotherapy in Gallbladder Cancer

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Gallbladder cancer (GC) is considered a rare disease associated with a poor prognosis. Unfortunately, the low number of cases makes the performance of trials addressing the role of adjuvant, neoadjuvant, and/or palliative therapy difficult. For a long time, the majority of trials were 5-fluorouracil (5 FU)-based, and results were uniformly poor. Since the introduction of Gemcitabine, response rates of approximately 30% have been observed through the use of this drug and new approaches have been tested. In this sense, drugs such as Cisplatin and Capecitabine have been employed concurrently with gemcitabine and/or radiation. Since a recurrence pattern is both distant and local, chernoradiation seems a logical option to deal with the disease. However, at the present time, the lack of valid and scientific evidence means that most of the recommendations originate from trials dealing with other tumors, such as pancreas cancer and biliary tract cancer (BTC). The aforementioned treatment alternatives warrant further evaluation focusing on GC.

KEY WORDS: gallbladder cancer; chemoradiotherapy; gemcitabine; metastatic disease

INTRODUCTION

In Chile, gallbladder cancer (GC) represents the main cause of death by malignancies in women, and is also a common tumor in men. This tumor also shows high rates in countries such as India, Bolivia, and Mexico [1–3].

Among the factors associated with the disease, gallstones are the most commonly described. Stones are observed in approximately 90% of Chilean patients with cancer [3].

Studying the cholecystectomy specimen is the most common way to detect early forms of the disease while exams such as the CT scan and MRI are frequently employed in the staging of advanced tumor [4]. Complete resection is the only potential curative treatment, but this therapy can be used in a proportion not higher than 30% of cases. In fact, a cholecystectomy is curative in patients with tumors in which invasion is restricted to the mucosa or muscular layer. Unfortunately no more than 30% of patients with tumors of the gallbladder have these early forms of the disease. In the rest, wall infiltration is deeper and prognosis is poorer [5,6].

Table I shows the distribution of tumors according to the level of wall invasion in a series of patients diagnosed at the Temuco Regional Hospital in Chile.

Gallbladder cancer is an uncommon disease in USA and Europe, where the majority of cancer therapy studies are performed. As a result, management protocols for GC are commonly extrapolated from studies of tumors of the pancreas and biliary tract. GC dissemination is thought to be mainly locoregional, thus the majority of therapeutic schemes are designed to control this area. Locoregional recurrence occurs along the resection margin, in the porta hepatis and in the retroperitoneal lymph nodes and it likely arises from microscopic residual disease [7]. However, from our observations and from other reports, we have acknowledged the importance of

Grant sponsor: Fondecyt Project; Grant number: 1050603.

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TABLE I. Distribution of Tumors According to Level of Wall Invasion

	Female	Male	Total	%
Histology				
Adenocarcinoma	709	122	831	98
Other	10	2	12	12
Infiltration level				
Mucosal	123	22	145	17
Muscular	71	12	83	9
Subserosal	162	21	183	22
Serosal	237	38	276	33
Beyond serosa	125	31	156	19

distant metastases in the control of the disease. Jarnagain [8] demonstrates the dissimilarities between GC and biliary tract cancer (BTC) when the patterns of recurrence are studied. GC, in contrast to BTC, has a propensity for distant involvement, whereas BTC recurs initially at the locoregional site [8]. In spite of this, and owing to the close relation of both GC and BTC, these tumors are generally managed in much the same way. This fact is exemplified in the case of radiotherapy, which is recommended and used frequently, although there is no data published that suggests an adjuvant approach oriented only to locoregional recurrence [8].

From the analysis of the dissemination pattern we can conclude that management of advanced GC requires the use of associated therapies in order to gain a more complete control of dissemination areas outside of those treated by surgery.

During the 1980s and 90s, a number of reports appeared on the effect of drugs such as 5-fluorouracil (5 FU) on the management of patients who presented with locally advanced BTC or with metastatic disease. These reports emphasized the poor results in both response and survival. Similarly disappointing results were reported with the use of other types of drugs, such as streptozocin, methyllomustine, m-amsacrine, and paclitaxel [9–11].

5-fluorouracil was the most commonly used drug in the treatment of GC. The preliminary results in both neoadjuvant and adjuvant therapies employing combined therapies in pancreas cancer was the rationale for its use in GC [12,13].

Only after Gemcitabine was used in the treatment of pancreas cancer and showed promising results, did it begin to be incorporated into GC management. This drug is a deoxycytidine analog that functions as an antimetabolite. Gemcitabine has been shown to be a potent radio sensitizer both in vitro and in vivo [14].

Neoadjuvanttherapy

This concept was suggested in pancreas cancer in 1980 by Pilpich, who reported 17 patients with unresectable tumors; one-third of them could undergo resection after pre-operative radiation [15]. In the same way, its use in rectal cancer showed a significant reduction in the rate of pelvic recurrence [16,17].

From a theoretical point of view, the employment of this type of therapy prior to surgery would have the following positive effects: (a) pre-operative radiotherapy could reduce the implantability of cancer cells shed during surgery; (b) the time elapsed during the course of radiotherapy would allow the possibility of performing a patient restaging, to identify patients with progressive metastatic disease, sparing them from an operation that would help little in the management of the disease; and (c) radiation toxicity is more effective in well oxygenated tissues that have not been rendered hypoxic as a result of surgery.

Later, Evans reported his experience with this therapy using radiotherapy associated with the infusion of 5 FU. The rationale for combined therapy is to exploit the concomitant effect of both 5 FU and radiation on the cancer cells [12].

Concerning BTC, external radiotherapy could increase resectability. McMasters et al. reported the effect of external radiotherapy on nine patients who were considered unresectable before the radiation but after the therapy could undergo resection [18]. In GC, we developed a prospective randomized trial to evaluate the effect of neoadjuvant chemoradiation on patients with GC. Eligible patients were those with a GC detected after the examination of the cholecystectomy specimen with a wall invasion deeper than the muscular layer. Patients allocated to chemoradiation received 5 FU in continuous infusion for 5 days at days 1 and 28 of treatment. Radiotherapy consisted of a total dose of 4,500 cGy, divided into 25 sessions. Patient survival was compared to a series of 19 patients not formerly subjected to chemoradiation. Twenty patients had hematological problems secondary to the therapy. Chemoradiation delayed surgical treatment in eight patients. After the chemoradiation protocol, seven patients were excluded from surgical treatment and 14 patients underwent resection. Three of the latter (11%) had liver involvement and four (14%) had lymph node involvement. Among the patients who underwent resection, five are still alive with a follow-up of 43.8 months. From the analysis of the results, we could conclude that in this series of patients, chemoradiation had no positive effect on survival [19]. However, this form of therapy is feasible and new trials could be developed to get more detailed information about this therapy.

Gemcitabine has been shown to provide survival advantage when employed in tumors like pancreas and gallbladder. Blackstock published his results with twice weekly gemcitabine treatments concurrent with external

beam radiation in patients with pancreas cancer. Gemcitabine was administered for 5 weeks in escalating doses of 20–60 mg/m2 until toxicity was reached. Hematological and gastrointestinal toxicity were dose limiting [20]. Unfortunately, the majority of reports include only a small number of patients with GC. Lin [21] reported a series of 42 patients with tumors of the pancreas, biliary tract and gallbladder, yet only one patient in this series had GC. A full course was administered to only 29 patients. The overall response rate was 24% (10 patients) [21].

To avoid the possible toxicity of the combination of gemcitabine and radiation, alternating cycles of gemcitabine and radiation with 1-week breaks placed between the two modalities was used.

Ammori et al. [22] published their results with gemcitabine associated to radiotherapy in a small series of patients. One of the main objectives of this trial was to evaluate the effect of this therapy on the complication rate after pancreatoduodenal resection. Although in this trial the number of patients was small (nine patients), complications were not increased by concurrent gemcitabine and radiotherapy. Furthermore, with respect to the effect of this therapy on the resectabilty rate: encouraging results were obtained in three patients thought to be unresectable at the time of the first laparotomy, but they could undergo resection after Gern/Rt with both nodes and margin negatives [22].

Postoperative Therapy

The rationale for postoperative chemoradiation therapy is to sterilize tumor cells areas surrounding the tumor that could be left after the surgery. The majority of experience in this area comes from studies performed in biliary tract and pancreas cancer.

Many institutions have reported improved outcomes with radiotherapy after radical resection. Improvement in survival would be due to a reduction in the rate of locoregional recurrence. In this sense, the European Organization for the Research and Treatment of Cancer reported a survival benefit in 38 patients with a Klatskin tumor who underwent external beam radiotherapy after curative resection versus 19 patients who only underwent resection [23].

A Japanese series of patients have shown similar results comparing patients with Klatskin tumors who underwent radiotherapy (intraoperative, or external postoperative) versus those who only underwent surgery. This benefit was observed in both the median survival rate and the recurrence rate [24].

On the other hand, Pitt et al. [25] did not show any benefit from adjuvant radiotherapy in a series of patients who underwent resection for biliary tract carcinoma. However, the number of patients was small and their characteristics too imbalanced to get any definitive conclusions [25]. Concerning pancreas cancer: the European Study Group for Pancreatic Cancer adjuvant trial (ESPAC-l) comparing chemotherapy to combined chemotherapy radiation versus surgery alone showed a significant benefit from adjuvant chemotherapy but none from chemoradiation [26]. These results challenge those obtained by other groups of researchers who have pointed out the value of using chemoradiation in a postoperative setting.

Unfortunately, most of the trials already published were performed using 5 FU [27]. Due to the results obtained in the ESPAC trial, the ESPAC-3 now in progress does not include radiation; rather, it compares three groups of patients after the resection of pancreas cancer: patients receiving 5 FU and leucovorin, those receiving gemcitabine and those receiving no therapy.

Concerning GC: a small number of studies have evaluated the role of adjuvant therapy. The Mayo Clinic reported its results in a series of 2l patients with completely resected GBC that resulted in higher 5-year survival compared with historic controls who underwent surgery alone.

This benefit was mainly observed when patients with no postoperative residual disease undergoing chemoradiation were compared with historic controls. Unfortunately, the number of potentially resectable cases is too low and distributed over too long a period of time (12 years) to get statistically significant results [28].

Another recent report from Duke University shows their experience in the management of 22 patients with resected and nonmetastatic adenocarcinoma of the gallbladder who underwent external beam radiotherapy as adjuvant therapy. Of the above patients, 12 (55%) had a complete resection with negative microscopic margins.

TABLE II. Adjuvant Treatment in Gallbladder and Billiary Tract Cancer

Author	GBC/BTC	Survival	Treatment	Comments
Kresal [28]	21/0	Median survival time: 33%	Chemoradiotherapy with 5 FU	Included patients with gross and no residual disease
Czito [29]	22/0	Median survival time: 37%	Chemoradiotherapy with 5 FU	Patients with microscopic residual disease had similar prognosis that without residual disease

TABLE III. Palliative Treatment in Gallbladder and Billiary Tract Cancer

Author	GBC/BTC	Survival	Treatment	Comments
Tsavaris [33]	14/14	Median survival time: 14 months	Weekly gemcitabine	GBC had better outcome than BTC 37.5% vs. 27.5%
Malik [32]	11/11	Overall survival 42 weeks	Gemcitabine and cisplatine	All had stage IV. No treatment-related death
Eng C [34]	9/6	Median overall survival 20 weeks	Gemcitabine	Myelosuppression
Patt Y [34]	8/18	Median overall survival 10.1 weeks	Oral capecitabine	Patients underwent cholecystectomy
Knox [39]	22/23	Median overall survival 14 weeks	Capecitabine and gemcitabine	Well tolerated therapy

Eighteen patients received concurrent 5 FU. In this series, patients with a microscopically positive margin after gross resection did not have any worse an outcome compared with those with a negative margin. This report advocates a radical resection followed by external beam radiotherapy with radiosensitizing 5 FU. However, the main drawback of this report is the low number of patients included in each group [29].

After analyzing the above-mentioned results, we have begun a new protocol of adjuvant therapy employing capecitabine associated to radiotherapy. This scheme is oriented to patients who underwent complete resection including lymph nodes and liver tissue that harbor poor prognosis factors such as lymph node and/or hepatic infiltration (Table II).

Palliative Management

There is an urgent need to identify drug combinations that can be effective in the management of advanced GC. Until recently, the majority of regimes were 5 FU-based. Whittington [27] published his results with BTC in a Phase I trial of a 5 FU infusion concurrent with radiation. He observed a median survival of 11.9 months and a 2-year survival rate of 19%. Kopelson [13] also published a report on the benefits of the concurrent use of radiotherapy and chemotherapy. As mentioned earlier, the introduction of Gemcitabine was associated with the first reports of higher responses. In phase II trials evaluating the single agent activity of gemcitabine in 20 patients with advanced BTC, objective response rates up to 60% have been described [30].

In Chile, Gallardo [31] reported the results of a series of 26 patients with metastatic and unresectable GC. In this series, he observed a 36% response rate and 30 months of median survival. Similarly to Gemcitabine, Cisplatin has also shown some effect in the control of the disease. The observation of synergism between Gemcitabine and Cisplatin provided the opportunity to use this combination in the management of advanced cases. Malik et al. [32] observed an impressive 64% response rate in a series of 11 patients with locally advanced metastatic gallbladder carcinoma. Although this rate has not been duplicated in other reports, rates between 9% and 53% have been observed [33–36]. In contrast to the Malik et al. [32] report, the majority of the previously cited reports all include BTC. This fact must be taken into account in the analysis because tumors of the gallbladder and biliary tract can behave differently with respect to the response to treatment.

Although the total number of patients has been small, the magnitude of the response rate, the good tolerance and the fewer side effects raise the possibility of using this combination in future trials. In the same way, the synergic effect of 5 FU with Gemcitabine and the absence of overlapping toxicity offer the chance for future combination trials [37].

Capecitabine, an orally administered systemic 5 FU prodrug, has been tested in GC. One of the main positive effects of this drug is its capacity to lead to 5 FU concentrations 125 times greater than serum concentrations in tumors. The effect of capecitabine on GC was evaluated by Patt [38], who showed a 50% response rate.

Finally, Knox et al. [39] reported one of the largest series in biliary cancer treated with the combination of Gemcitabine and Capecitabine. In this report, both BTC and GC were treated. In both types of tumors response rates of approximately 30% were observed. In the same way, tolerance to this drug combination was good even in patients with liver dysfunction and/or biliary stents [39] (Table III).

CONCLUSION

Gallbladder cancer is an uncommon disease in the United States and Western European countries and little research has been conducted to gain clearer insights into its management.

Surgical therapy currently offers the only potential cure for this tumor. Unfortunately, the majority of patients present with advanced tumors with no chance of a curative resection; moreover, those who undergo a potentially curative resection harbor poor prognosis factors that increase the chance of failure.

For a long time the lack of effective drugs and the modest results obtained made the design of management protocols for this disease more difficult.

The appearance of Gemcitabine and Cisplatin and their first results in pancreas cancer made possible the development of protocols for the treatment of GC.

Currently, there is evidence mainly extrapolated from pancreas cancer and from small series of patients regarding the value of the above-mentioned drugs in the management of advanced GC in a palliative setting. However, it is necessary to study factors such as dose, concurrent use of radiotherapy, and drug association. As to neoadjuvant and adjuvant therapy: from a theoretical point of view, the association of radiotherapy and chemotherapy seems to be a reasonable alternative. Based on the recurrence patterns, it is difficult to advocate the use of radiotherapy alone. Instead, the addition of chemotherapy would be essential for improving results.

In adjuvant therapy, the development of trials such as the ESPAC-I performed in GC would be necessary to address the real effectiveness of adjuvant therapy. This method of trial would be important given the conflictive results obtained by the ESPAC-I that challenged the real value of radiotherapy associated to chemotherapy.

Concerning neoadjuvant chemotherapy: it is necessary to know the real value of this therapy to down stage the disease and make resectable a previously unresectable disease. Unfortunately the lack of controlled studies makes it difficult to accomplish this objective.

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