CORRESPONDENCE

Efficacy of Gemcitabine in the Treatment of Patients with Gallbladder Carcinoma

A Case Report

Castro's case report of examining the significant antitumor action of gemcitabine against advanced, previously chemotherapy-resistant metastatic carcinoma of the gallbladder in the absence of significant side effects is a rare ray of hope for patients with this usually rapidly progressing, intractable disease.[1] However, Castro's comment that " . . .carcinoma of the biliary tract is a rare disease . . ." requires qualification. Although this disease accounts for $<$ 1% of deaths from cancer in the U.S.,[2] it is the leading cause of death from malignant neoplasia in women in Chile and is increasing (11.6 to 16.2 deaths per 100,000 population for 1982 and 1991, respectively).[3] Other Latin-American countries have similar frequencies.[4]

In our Oncology Center[5] 88% of gallbladder carcinoma patients are female, with an average age at diagnosis of 57 years for females and 63 years for males. Approximately 65% of diagnoses are made intraoperatively and nearly 100% of cases are adenocarcinomas. The average survival for patients with advanced disease is 3.9 months, and the most effective therapy has been surgical resection, although this is seldom curative. Through 1997 we used 5-fluorouracil (5-FU) alone or in combination with leucovorin, with a response rate of 26%.

Based on our poor experience with these therapeutic interventions, the presentation of data demonstrating the effectiveness of gemcitabine in pancreatic carcinoma,[6] and the common embryologic origin of the exocrine pancreas and the gallbladder, we began trials of gemcitabine therapy. One patient was treated in 1997 and a formal Phase II trial was initiated in January 1998. For patients with locally advanced or metastatic disease, the gemcitabine therapy regimen was comprised of 1.0 g/m^2 over 30 minutes weekly for 3 weeks followed by 1 week off treatment. The patient treated in 1997 underwent previous surgery followed by chemoradiation and then 5-FU and leucovorin followed by 5-FU continuous infusion (CI) (all treatments induced a partial response that was followed by disease progression). At last follow-up, this patient had been treated with gemcitabine for 8 months. He had a partial response followed by stable disease. During treatment he continued to work and had few adverse symptoms. We seldom have observed such long term survival and it is especially noteworthy considering the failure of three preceding treatment regimens.

At last follow-up three patients had been enrolled into the Phase II protocol and two of them had completed two treatment cycles. All patients experienced a prompt remission characterized by significant relief of pain and increased performance status. Data regarding tumor size were available for the patients who completed two cycles; in both patients a decrease in the size of the tumor was documented (Figs. 1 and 2). Toxicity was mild.

To our knowledge the limited reports regarding gemcitabine ther-

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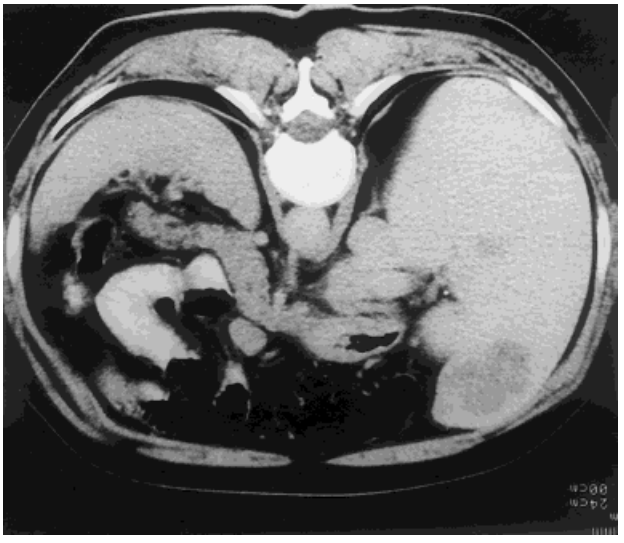

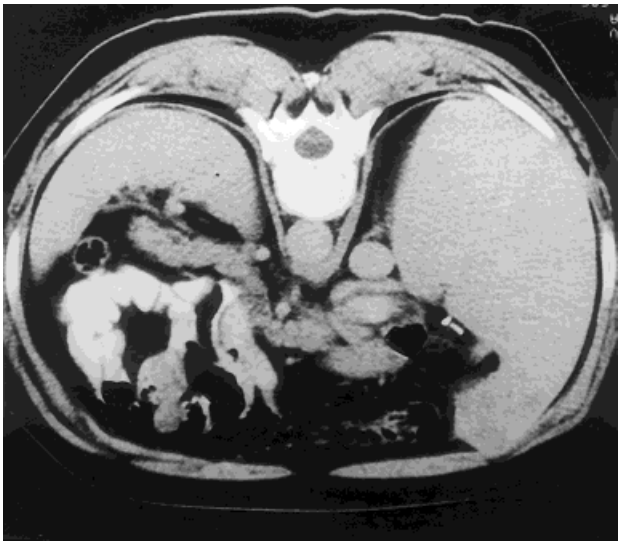

FIGURES 1 AND 2. CT scan of one patient who completed two cycles of gemcitabine showing a decrease in the size of the tumors.

apy for advanced gallbladder carcinoma are more uniformly positive than are results obtained with any established treatment regimen. We agree with Dr. Castro that detailed clinical trials should be undertaken rapidly to determine definitively the utility of gemcitabine for gallbladder carcinoma. In addition, we share the concern expressed by Dr. Castro that the low prevalence of gallbladder carcinoma in regions in which the majority of clinical trials are conducted may continue to result in very limited resources being deployed to this end.

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The comments of Dr. Gallardo et al. are most welcome. Their early experience with gemcitabine in the treatment of gallbladder carcinoma gives hope that an effective treatment for this disease will emerge in the near future. If the efficacy of gemcitabine can be demonstrated in their clinical trial, we would have further proof that anecdotal observations do provide fertile ground for testing new hypotheses and should not be discounted as routinely occurs in medicine.

The high rates of carcinoma of the gallbladder in Chile and other parts of Latin America constitute an opportunity for more accelerated treatment experience than exists in the U. S., thereby giving us an opportunity to learn from our southern neighbors. Hopefully, this opportunity will not be missed by practitioners, nor by would-be sponsors of clinical trials.

Combination chemotherapy trials with gemcitabine already are underway, and also may be worthy of consideration for gallbladder carcinoma. Improvement on single agent results with concurrent use of gemcitabine and cisplatin in nonsmall cell lung carcinoma is a noteworthy example. The combination of doxorubicin and gemcitabine recapitulates the model of an anthracycline combined with cytarabine, the first major treatment success in acute myelogenous leukemia, and therefore also would be worthy of testing in solid tumors. The imminent availability of monoclonal antibodies such as Herceptin (Genentech, Inc.) and anticarcinoembryonic antigen antibody, and their synergistic combination with cytotoxic agents

could be applicable to many patients with gallbladder carcinoma, representing yet another novel and promising idea for testing in the coming years. Finally, given the propensity of both gallbladder and pancreatic malignancies to spread to the peritoneal cavity, the feasibility and usefulness of intraperitoneal administration of gemcitabine should be explored as well.

Clearly, much work remains to be done for this difficult disease, but perhaps the new and expanding array of tools in oncology gradually will allow our hopes to be translated into reality.

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Thyroid Papillary Carcinoma of Columnar Cell Type

A Clinicopathologic Study of 16 Cases

We read the report by Wenig et al.[1] regarding 16 cases of thyroid papillary carcinoma of columnar cell type in which the authors referred to our article on poorly differentiated forms of papillary carcinoma,[2] making some objections that we would like to debate.

The concept of poorly differentiated carcinoma has been in use since 1983[3] and according to the literature[3–5] these tumors represent the least differentiated forms among differentiated carcinomas of the thyroid, both papillary and follicular, and strongly differ from undifferentiated carcinoma in terms of morphology, immunophenotype,[6] and clinical outcome.

Columnar cell carcinoma is believed to belong to this group and therefore is expected to show a more aggressive behavior. However, one either accepts or rebuts this categorization; to find any difference one must perform a comparison study. Because the authors studied only columnar cell carcinomas, their conclusion that such tumors share the same characteristics as typical papillary thyroid carcinoma is not tenable. By contrast, we studied 227 consecutive cases of papillary carcinoma that were reclassified according to updated criteria and subjected to statistical analysis to verify whether the presence of a histologic pattern consistent with poorly differentiated forms of papillary carcinomas (pPDCs), such as the tall cell (TC) and columnar cell (CC) variants, also carried a prognostic value. The comparison between well differentiated papillary carcinomas (PCs) (n = 184) and pPDCs (n = 44) with logistic regression showed a statistically significant association between differentiation and age $>$ 40 years, extrathyroid tumor extension (pT4), and a low ratio of regional lymph node involvement at the onset of disease. In addition, differentiation, as represented by pPDCs, was found to be the strongest predictor of biologic behavior, with recurrences and recurrence-related deaths being 5-fold and 20-fold higher, respectively, in this group with respect to PCs.

In our study we did not match tumors for size because, applying the pT classification,[7] it is well known that the pT4 category represents a stronger factor than size. Furthermore, because we included microcarcinomas (pT1 tumors) among both PCs and pPDCs tumors, no bias may be ascribed to our results. Regarding the matched "growth characteristics," we consider TCs and CCs as a whole because our aim was to ascertain the prognostic power of "differentiation" and CC, similar to TC, bears poor differentiation features. Along these lines, encapsulated papillary carcinomas were included among PCs. With regard to the three cases showing mixed TC-CC features and suggesting a close relation between the two variants, we share the hypothesis already suggested by others.[8]

In addition to the fact that it is unclear what Wenig et al. mean by "papillary carcinoma with insular growth pattern," because papillary features are well known in insular carcinoma, we wonder how they can question insular carcinoma when their study is restricted to 16 cases of CC. In any case, it is worth mentioning that even insular carcinoma appears to represent a PDC according to an early suggestion by Carcangiu et al.,[4] and one of our own recent surveys.[9]

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In our recently published series of 16 cases of columnar cell types of papillary carcinoma,[1] we included a critique of an article by Pilotti et al.[2] in which those authors found the so-called "poorly-differentiated types" of papillary carcinoma, including the columnar cell and tall cell types, to be distinct morphologic types with uniformly aggressive biologic behavior. The findings of Pilotti et al.[2] then would indicate that all thyroid papillary carcinomas with the morphologic characteristics of columnar or tall cells irrespective of size or extent of invasion should be considered and treated as aggressive thyroid carcinomas.

In a correspondence regarding our article on the columnar cell type of thyroid papillary carcinoma,[1] Pilotti et al. state that the conclusions we drew relative to the biologic behavior of the columnar cell type of papillary carcinoma are untenable owing to the absence of a statistical comparison with other thyroid papillary carcinomas. These authors state that to make a valid comparison a statistical correlation is required similar to the one that they performed in their study.[2] It is true that in our article we did not include a statistical comparison with other types of papillary carcinoma. However, we would argue that a statistical comparison, although preferable, is not necessary to arrive at the conclusions we made in our article and the absence of statistical correlation does not invalidate our findings.

Pilotti et al.[2] continue to hold to the concept that the columnar cell type of papillary carcinoma (and for that matter the tall cell type) is a poorly differentiated tumor simply on the basis of cell type. However, we would ask what are the histologic features that define these tumors as poorly differentiated? In their letter to us, these authors fail to indicate what these "poorly differentiated" features represent but cite three other articles to support their contentions. The first of these three cited articles is by Sakamoto et al.,[3] who separated well differentiated from poorly differentiated papillary carcinoma on the basis of whether a tumor had gland formation. These authors indicate that "When nonglandular components were found in papillary and follicular carcinomas on histologic examination, the tumor was denominated poorly differentiated carcinoma."[3] We cannot accept this definition for a poorly differentiated thyroid carcinoma because solid, nonglandular foci can be observed in nonneoplastic lesions of the thyroid (e.g., dyshormonogenetic goiter), in benign thyroid tumors (e.g., hyalinizing trabecular adenoma), and in thyroid malignant tumors that behave indolently (e.g., minimally invasive follicular carcinoma and papillary carcinoma). According to the Rosai et al.,[4] there are several histologic parameters that define a poorly differentiated thyroid carcinoma, including (but not limited to) the presence of nuclear pleomorphism, mitotic activity, and necrosis. None of these features were used by Sakamoto et al.[3] in their study on so-called poorly differentiated thyroid carcinomas.

The next study cited by Pilotti et al. in their letter is the article by Carcangiu et al.[5] regarding the thyroid "insular carcinoma." It has been shown clearly by other authors[6,7] that an "insular" growth pattern does not in and of itself equate a poorly differentiated thyroid carcinoma nor does the presence of an insular growth confer an aggressive behavior to any thyroid neoplasm. Therefore, insular carcinoma should not be included uniformly as a poorly differentiated carcinoma simply on the basis of having an insular growth pattern. This is not to indicate that there are not aggressive-behaving thyroid carcinomas with insular growth. The latter do exist but in addition to an insular pattern includes the presence of necrosis, increased mitotic activity, and invasive growth. Pilotti et al. ask "how [the authors] can question insular carcinoma when their study is restricted to 16 cases of CC (*columnar carcinoma,* our addition)." We included insu-

lar carcinoma in our study of columnar cell carcinomas to refute the concepts that the biologic behavior of thyroid tumors should be predicated solely on the growth pattern (i.e., insulae) or on the cell type (i.e., columnar or tall.) To this end, we indicate that thyroid lesions not considered within the scope of "insular carcinoma" nonetheless may have an insular growth and that these lesions do not behave aggressively. Our findings (sans statistics) more than adequately refute these erroneous concepts, including those cited in reference 5 of Pilotti et al.'s correspondence in which Sobrinho-Simões et al. indicate that columnar cell carcinomas are poorly differentiated tumors. In their letter, Pilotti et al. state that "papillary features are well known in insular carcinoma." We would agree that "insular carcinomas" are not restricted to the category of follicular carcinomas and that papillary carcinomas also may demonstrate an insular growth pattern.[5] However, there remain some unresolved issues relative to thyroid tumors with insular growth, including classification. According to the World Health Organization Committee on the classification of thyroid tumors, insular carcinoma is considered a morphologic variant of follicular carcinoma.[8]

The clinicopathologic features of the columnar cell and tall cell types of thyroid papillary carcinoma have not been defined completely. Not the least of the issues revolving around these tumor types is what exactly is a "tall" cell. For unexplained reasons, many studies reporting on the columnar and tall cell types of papillary carcinoma demonstrate the fact that these tumor types tend to occur in older patients with extrathyroidal extension of their tumor. We agree with Pilotti et al. that pT4 thyroid tumors, defined as a tumor of any size extending beyond the thyroid capsule, represents a stronger factor in predicting prognosis than tumor size. We would extend this argument to state that this applies to all thyroid papillary carcinomas irrespective of cell type such that pT1 columnar cell types of papillary carcinoma behave no differently from pT1 usual papillary carcinomas, and so forth. This matching of different types of papillary carcinoma in each pT category was not done by Pilotti et al.[2] Furthermore, nowhere in their letter did Pilotti et al. discuss the other recently published studies showing that columnar cell carcinomas are not uniformly aggressive tumors but will behave in an indolent manner if they are encapsulated, have limited invasion, and do not show extrathyroidal invasion.[9,10] These findings support the contentions of our study[1] and validate the fact that the behavior of all types of thyroid papillary carcinoma are based on features other than cell type (i.e., columnar, tall, oxyphilic, etc) growth pattern (i.e., insular). Our findings as well as those of other authors[9,10] dispute statements such as those made by Pilotti et al. indicating that " . . .the categorization of a carcinoma as poorly differentiated papillary carcinoma, or as one of the three variants that belonging to the group (*including columnar cell, tall cell, and mixed type,* our addition), clinically implies the presence of a high risk tumor."[2] We feel completely justified in making the point that each patient's thyroid papillary carcinoma, irrespective of growth pattern or cell type, should be evaluated on its own and not lumped within a category of tumors that clearly do not uniformly follow an aggressive biologic course. Our findings validate this point and show that the columnar cell type of thyroid papillary carcinoma is not necessarily a distinct biologic entity separate from the usual morphologic types of papillary carcinoma.

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