The association between tamoxifen and the development of hepatocellular carcinoma: case report and literature review

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Tamoxifen has become one of the most widely used drugs in the treatment of breast cancer, and concerns about its long-term safety and efficacy are being raised. Investigations in rats have suggested an association between the administration of tamoxifen and the development of hepatocellular carcinoma. However, no studies to date have demonstrated an increased incidence of hepatocellular carcinoma in women treated with tamoxifen. In the case reported, a 56-year-old woman presented with hepatocellular tumours after 6 years of tamoxifen therapy for breast cancer. The patient had no other risk factors for the development of hepatocellular carcinoma. She underwent successful resection of the lesions, and subsequent pathological studies confirmed hepatocellular carcinoma with a trabecular growth pattern similar to the histologic pattern seen in tamoxifen-induced hepatocellular carcinoma occurring in rat models.

Le tamoxifène est devenu un des médicaments les plus répandus dans le traitement du cancer du sein et sa sécurité et son efficacité à long terme préoccupent. Des études réalisées sur des rats indiquent qu'il y a peut-être un lien entre l'administration de tamoxifène et l'apparition du carcinome hépatocellulaire. Aucune étude n'a toutefois démontré jusqu'à maintenant d'incidence accrue du carcinome hépatocellulaire chez les femmes traitées au tamoxifène. Dans le cas qui fait l'objet du rapport, une femme âgée de 56 ans avait des tumeurs hépatocellulaires après avoir suivi pendant six ans un traitement au tamoxifène contre le cancer du sein. La patiente ne présentait aucun autre facteur de risque d'apparition du carcinome hépatocellulaire. Elle a subi une résection réussie des lésions et des analyses pathologiques subséquentes ont confirmé la présence d'un carcinome hépatocellulaire avec excroissance trabéculaire semblable à l'évolution histologique constatée dans les cas de carcinome hépatocellulaire provoqué par le tamoxifène chez des modèles murins.

Tamoxifen, a nonsteroidal triphenylethylene derivative having a chemical structure similar to diethylstilbestrol, is currently used as an antiestrogen in the treatment of breast cancer as primary and adjuvant therapy. However, several recent studies showed that women treated with tamoxifen had a lower incidence of second or contralateral breast cancer.[1–3] These data prompted trials of tamoxifen as a chemopreventive agent in women at risk for the development of breast cancer.[4] A 2-year safety evaluation study conducted by the manufacturer of tamoxifen has shown that liver tumours develop in rats exposed to tamoxifen.[5] More recent studies continue to confirm the hepatoproliferative and carcinogenic properties of tamoxifen in rats.[6–8] A recent review of 9 population-based cancer registries in the United States attempted to determine if there has been any change in the incidence of hepatocellular carcinoma since 1977, the year that the US Federal

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Drug Administration licensed tamoxifen for use.[9] This study did not show any increase in the incidence of hepatocellular carcinoma in this group; however, the results can be questioned owing to a number of confounding factors. We present a case in which hepatocellular carcinoma developed in a patient who had been on long-term tamoxifen therapy.

Case report

A 56-year-old woman who was undergoing radiologic investigation of recurrent pneumothoraces was found to have 2 masses in the liver: a 9.0-cm mass in the lateral segment and a 1.5-cm mass in the caudate lobe. Her α-fetoprotein level was elevated to 4860 μg/L and a subsequent needle biopsy was suspicious for hepatocellular carcinoma. Her history included a bilateral lumpectomy and left axillary node dissection for invasive ductal carcinoma of the breast 9 years earlier. From 1989 to 1995 she received tamoxifen (20 mg/d) as adjuvant treatment. She also had undergone cholecystectomy, hysterectomy and a hiatus hernia repair. She did not have any history of oral contraceptive use, hepatitis, blood transfusions or significant alcohol intake. Her hepatic synthetic function was normal, and hepatitis B and C serologic findings were negative. Intraoperative ultrasonography confirmed that there were no other lesions in the liver, and an uncomplicated left lateral segment and caudate lobe resection was performed. She was discharged from hospital on the fifth postoperative day. Histologic examination of the resected specimen confirmed hepatocellular carcinoma in a trabecular growth pattern. The surrounding liver was entirely normal grossly and histologically. At her 6-month follow-up, she was doing well with no radiologic or laboratory evidence of recurrence.

Discussion

Tamoxifen is one of the most widely used chemotherapeutic agents in the world. Its success in increasing survival when used as an adjuvant agent as well as its tendency to reduce the incidence of contralateral breast cancer has inspired the hope that it will act as a chemopreventive agent in women considered to be at high risk for breast cancer. The National Adjuvant Surgical Breast and Bowel Project (NSABP) has recently published the results of the Breast Cancer Prevention Trial (P-1), reporting a decreased incidence of breast cancer in women with significant risk factors while taking tamoxifen.[10] Other clinical trials are also under way,[4] but the actual reduction in risk of breast cancer may require up to 5 years of tamoxifen therapy.

Animal studies have been limited mainly to rats, in which tamoxifen has been confirmed as a factor in the development of hepatocellular carcinoma. Studies show that tamoxifen given orally results in the formation of DNA adducts. A high number of adducts are found in those rats in which hepatocellular carcinoma subsequently develops, suggesting a causal relationship.[6–8] Several interesting observations were noted by Carthew and associates.[7] First, they found that DNA adduct formation is not only dose-dependent but also time-dependent in the rat. Previous criticisms of rat studies focused on the higher relative doses used in rats than in humans. Second, they noted that there was a significant difference in biologic response between strains of rats. Fischer rats did not undergo as much liver proliferation in response to tamoxifen at the same time periods as did corresponding Wistar and Lewis rats. In addition, they did not progress from foci of proliferation to carcinoma during the study period. These data suggest a possible pharmacogenetic component to tamoxifen-induced hepatocellular carcinoma.

Hepatocellular carcinoma can have a wide variety of histologic patterns ranging from trabecular, sclerosing and fibrolamellar to the arrangement of compact sheets as seen in the anaplastic type. In the rat models, the trabecular pattern of hepatocellular carcinoma was noted uniformly in the tamoxifen-induced tumours.[6] Histologic examination of the tumours from the patient in this report also revealed the trabecular pattern.

In general, hepatocellular carcinoma is relatively uncommon in humans. In Canada, the age-adjusted rates per 100 000 people are 2.0 for men and 0.8 for women.[11] Mühlemann and colleagues[9] reviewed the breast cancer population in 9 registries in the United States, looking for evidence of an increased rate of hepatocellular carcinoma in those patients who had been on long-term tamoxifen since its introduction in 1977. Unfortunately, the use of tamoxifen and the dose of tamoxifen were not directly analysed in that study. Instead a subgroup of women with breast cancer and older than 50 years were examined, this being the group most likely to have received tamoxifen. There is no way to know exactly what proportion of women in these groups actually received tamoxifen after 1977. In addition, there was no accounting of women who presented with "hepatic metastases" without a histologically proven diagnosis. It may also be too early to see any longer term hepatic effects from previous tamoxifen use.

Current data from larger trials involving tamoxifen have not documented any increase in the incidence of hepatocellular carcinoma to date. The combined results of the Stock-

holm Trial, the Danish Breast Cancer Group Trial and the South-Swedish Trial, involving 4914 patients, did not demonstrate any significant difference in the incidence of hepatocellular carcinoma between the tamoxifen and control groups.[12] In those studies, 4 patients in the tamoxifen group and 3 patients in the control group had hepatocellular carcinoma. Data from the NSABP Protocol B-14,[13] involving 2843 patients, did not report any cases of hepatocellular carcinoma, and neither did the Manchester study, which involved 961 patients.[14] Moreover, the recent BCPT did not report any case of hepatocellular carcinoma.[10]

There is concern that cases of hepatocellular carcinoma in these trials may have been misinterpreted as hepatic metastases from the known breast carcinoma without histologic confirmation. Unfortunately, data regarding the incidence of hepatic metastases in these large trials is incomplete. The Danish Breast Cancer Group Trials (DBCG 77 C and DBCG 82 C) did not report the number of distant metastases or the location of distant treatment failures.[15] The Stockholm Breast Cancer Group Trials showed no statistical difference in the number of distant metastases among patients treated with adjuvant radiotherapy (103 of 311 patients) versus adjuvant tamoxifen (141 of 395 patients).[16] The NSABP Protocol B-14 also showed no difference in the number of "other distant recurrences" between placebo (19 of 1326) and tamoxifen (19 of 1318).[17] Information regarding the location of distant recurrence or the number of new liver lesions in each group was not available in any of the above studies. Whether histopathological confirmation of the distant recurrence was made is not known either.

In humans, a single previous case report of hepatocellular carcinoma developing after a diagnosis of breast cancer and initiation of tamoxifen has been reported by Johnstone and associates.[18] However, the diagnosis of hepatocellular carcinoma was made only 6 months after the initiation of adjuvant therapy for her breast cancer and the patient was also taking numerous chemotherapeutic agents carrying their own risk of carcinogenesis.

There has been concern from published reports that oral contraceptive users had a relative risk of 2.6 for hepatocellular carcinoma and increasing risk with long-term use.[19] The concern for tamoxifen related to the fact that although the drug had mainly antiestrogenic effects for the breast, there was some evidence of estrogenic properties.[20]

Summary

Since tamoxifen has been established as a successful drug in the fight against breast cancer, concern has arisen that it may induce other tumours. The development of hepatocellular carcinoma reported in rat experiments is alarming. Although these findings do not necessarily translate directly to human effects, they may serve as a warning for maintained vigilance in the investigation of tamoxifen as a carcinogen. Currently, none of the larger trials utilizing tamoxifen has demonstrated any increase in the incidence of hepatocellular carcinoma. However, it is unclear whether a biopsy has been taken in patients with presumed hepatic metastases to rule out hepatocellular carcinoma. The case presented here demonstrates the development of hepatocellular carcinoma in a patient on tamoxifen who had no other risk factor for the development of the disease. Although a mechanism linking tamoxifen and hepatocellular carcinoma has yet to be discovered, future studies may help to identify a subgroup of patients who may be susceptible to a tamoxifen-induced hepatocellular carcinoma.

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