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ORIGINAL RESEARCH

Weekly cisplatin may reverse liver dysfunction and jaundice caused by diffuse liver metastases of solid tumors

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Abstract: Few data are available on patient management in jaundice caused by liver metastases of solid tumors (nonbreast and noncolon origin). We report the first patient series consecutively treated with cisplatin weekly in patients with severe jaundice and liver failure due to underlying metastatic neoplasms. In 4 out of 8 cases, liver function tests were reversed and jaundice disappeared, permitting subsequent standard chemotherapy. The other 4 patients died 3 to 5 weeks after admission, illustrating the extent and severity of the underlying neoplasm.

Keywords: liver failure, jaundice, metastases, chemotherapy, cisplatin

Introduction

Advances in chemotherapy and cytostatic drug pharmacology have made it possible for cancer patients with severe end organ failure to be treated with adapted drugs. Reports of patients with jaundice due to colon cancer,[1] lymphoma,[2] breast[3] and other tumor types[4–9] are becoming more frequent. This knowledge has been drawn from a deeper insight into the pharmacology of drug clearance in cancer patients with liver dysfunction.[10] Apart from case reports,[11] however, there are no reports of series of patients presenting with severe jaundice, due to metastatic involvement of the liver, in which the treatment and outcome are summarized. We report here the first case series in this patient group, in which all patients were treated the same way with weekly cisplatin, until recovery of liver function, or death. Our study aimed to demonstrate that even in these patients, a relatively well tolerated drug like cisplatin may reverse the jaundice and liver failure, permitting further more classical chemotherapies.

Methods

This was a retrospective study conducted at Sint-Maria Hospital of Halle, Belgium. All medical records provided by the Hospital Tumor Registry were screened by one investigator to identify patients who met the study team's a priori selection criteria. These criteria included severe hyperbilirubinemia, due to unresectable metastatic cancer, and no prior cancer therapy (no prior surgery, or radiation, or chemotherapy).

The medical records of the patients identified in this screening process were then reviewed in depth: namely, date of diagnosis, dates of cisplatin treatment, subsequent laboratory changes and further treatment or death.

Patients were considered eligible if they had imaging studies (CT and ultrasound) with evidence of liver metastases of different types of carcinoma and exclusion of biliary tract obstruction. All included patients also had serum bilirubin levels higher

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than 2.0 mg/dL. Patients were required to have: WHO performance score 1 to 3; neutrophil count >1500 mm³; platelet count >100,000; and normal serum creatinine at screening before starting chemotherapy. Eight patients were recruited, 4 men and 4 women.

Tumor responses were not assessed because of inconsistent patterns in radiographic testing from patient to patient and because of the greater value placed on survival.

Patients received 75 mg/m² cisplatin on days 1, 8 and 15 on a 4-week cycle, repeated on days 8, 22, 29 and 36, as described by van den Burg.[12] Patients with small cell lung carcinoma received subsequent therapy with etoposide, cisplatin and cyclophosphamide;[6] those with unknown primary had subsequent therapy with carboplatin and taxol weekly.[13]

Physical examination, vital signs assessment, body surface area calculation, biochemistry and hematology tests, and adverse-event assessment were performed prior to each dose of chemotherapy. Myeloid colony-stimulatory factors were not used because of the limited myelosupression of cisplatin.

Results

Patient characteristics are shown in Table 1. Liver tests at baseline and prior to each treatment cycle are shown in Table 2.

Four patients died after 2 or 3 cycles of treatment because of progressive cancer. The remaining 4 patients completed treatment with 4 to 6 cycles of cisplatin and received subsequent therapy adapted to the tumor type (Table 2). The most frequently reported adverse events were neurotoxicity, ototoxicity and anemia.

All patients initially showed a further rise of serum bilirubin with subsequent normalization of bilirubin after administration of second cycle of cisplatinum, as shown in Table 2. Alkaline phosphatase and alanine aminotransferase followed the same evolution as bilirubin.

Two patients remain alive at time of writing, more than16 months and 4 months, respectively. Median overall survival was 127 days.

Discussion

This study assessed the efficacy of treatment with weekly cisplatin in liver failure due to liver metastasis of common solid tumors. Weekly cisplatin was proven to be efficacious in diverse tumor types such as NSCLC,[14] head and neck cancer,[15] and ovarian cancer.[16] Its unique renal elimination permits administration in patients with severe jaundice and subsequent poor liver function.[17,18] The results of this retrospective analysis suggest that 4 to 6 courses of weekly cisplatin rapidly lead to normalization in serum bilirubin and other liver tests, which permits subsequent chemotherapy with cytotoxics with hepatic metabolism such as etoposide, cyclophosphamide and taxanes. Four patients died after the first administration, mostly due to concomitant pulmonary disease and low WHO performance score at baseline. Other side effects were related mainly to platinum-induced toxicities like anemia and ototoxicity. There were no treatment delays due to myelosuppression. The most well known side effect of cisplatin, namely vomiting and nausea, was vigorously prevented by administration of granisetron, aprepitant and steroids. As noted in the initial publication,[12] there were no cases of renal insufficiency due to the nephroprotective effect of hypertonic saline in which the cisplatin was dissolved. All 4 surviving patients had normal serum creatinine during cisplatin treatment and this did not change during later chemotherapies.

Unfortunately, it was not feasible to incorporate quality of life measures into this pilot study. Larger studies of this regimen in this patient group should include such measures in an attempt to assess the risk/benefit ratio for this palliative treatment.

Prior publications and case series as well as the current series underline the growing interest of oncologists in treating these patients whose prognosis is dismal without

Table 1 Patient characteristics

Patient No	Age (years)	Sex (m/f)	Tumor type	Survival	Start date	Date of death
1	65	m	SCLC	360 days	3/1/2004	4/9/2005
2	53	f	Papillar serous ovarian cancer	350+ days	8/2/2008	Alive
3	84	m	SCLC	3 days	11/18/2005	11/21/2005
4	69	m	SCLC	210 days	8/16/2003	4/3/2004
5	80	f	ACUP with liver M+	38 days	9/23/2005	11/8/2005
6	57	f	ACUP with liver M+	150 days	3/23/2000	8/1/2000
7	59	m	Undifferentiated lung carcinoma with liver mets	20 days	21/08/08	9/9/2008
8	66	f	Advanced cholangiocarcinoma	110+ days	6/26/2009	Alive

Abbreviations: ACUP, adenocarcinoma of unknown primary; SCLC, small cell lung cancer; M+, metastases.

Table 2 Evolution of biochemistry during consecutive cisplatin courses

Patient no	Test	Before cisplatin cycle (number)						
		1	2	3	4	5	6	
1	Bilirubin (mg/dL)	4.2	5.01	4.81	1.98	0.98	further chemo + cisplatin,	
	AP (U/L)	808	908	804	500	208	etoposide and	
	γ-GT (U/L)	1474	1662	1540	873	236	cyclophosphamide	
2	Bilirubin (mg/dL)	3.66	10.92	2.83	1.32		further treatment with oral etoposide	
	AP (U/L)	1546	1623	1021	315			
	γ-GT (U/L)	1986	1632	1020	256			
3	Bilirubin (mg/dL)	5.59	7.92	death				
	AP (U/L)	449	445					
	γ-GT (U/L)	797	793					
4	Bilirubin (mg/dL)	5.6	death					
	AP (U/L)	166						
	γ-GT (U/L)	182						
5	Bilirubin (mg/dL)	0.85	2.21	0.45	death			
	AP (U/L)	483	452	131				
	γ-GT (U/L)	776	989	207				
6	Bilirubin (mg/dL)	2.49	7.2	1.52	1.1	1	0.91	further treatment +
	AP (U/L)	457	622	309	198	153	124	cisplatin/paclitaxel
	γ-GT (U/L)	272	444	202	149	113	82	
7	Bilirubin (mg/dL)	2.24	5	5.43	death			
	AP (U/L)	1386	1158	782				
	γ-GT (U/L)	871	968	713				
8	Bilirubin (mg/dL)	10.01	10.56	3.59	1.95	1.41	0.93	further treatment +
	AP (U/L)	355	355	455	269	138	105	cisplatin/gemcitabin
	γ-GT (U/L)	682	648	1365	884	450	249	

Abbreviations: AP, alkaline phosphatase; γ-GT, gamma glutamyl transferase.

chemotherapy in all series. Our patient series is unique because it represents the first series of patients with fewer chemotherapy-sensitive tumor types than those mentioned above, who were all treated with the same cytostatic. The pharmacologically driven administration of a well known cytostatic, such as cisplatin, with its clinical efficacy even in severe jaundice, is paramount to success and prolonged survival in a substantial number of patients.

Conclusion

This is the first reported series of 8 patients treated with weekly cisplatin for diffuse metastases of solid tumors causing severe jaundice (not metastases caused by colon or breast cancer). Although there were a significant number of early deaths, in 4 of our 8 patients liver function recovered sufficiently to enable further standard chemotherapies. Because of the rarity of the presentation and the poor general state of these patients, this series may serve as a basis for further treatments and observations.

Disclosures

The authors declare no conflicts of interest.

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