Pergamon

European Journal of Cancer Vol. 33, No. 2, pp. 209–213, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00365-6

Original Paper

Bile Duct Stents: Is There an Increased Rate of Complications in Patients Receiving Chemotherapy?

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The aim of this study was to determine whether palliative chemotherapy accelerates the rate of biliary stent occlusion, in patients with a malignant biliary obstruction. Such treatment can induce neutropenia and increase the risk of bacterial sepsis. Overgrowth of bacteria within the bile of patients receiving chemotherapy could accelerate the rate of stent occlusion. Retrospective analysis of treatment records for 80 consecutive patients with a diagnosis of adenocarcinoma arising from the pancreas, bile ducts or gall bladder was conducted. Two groups were identified, those with a biliary stent *in situ* (primary stent group: 47/80; 59%) at the time of referral and those without (no stent group: 33/80; 41%). The majority of patients went on to receive chemotherapy, 64% and 70% in the primary stent group and no stent group, respectively. The rate of febrile neutropenia was similar in the two groups (5% versus 7% of all chemotherapy cycles in the primary stent group and no stent group, respectively). The rate of stent occlusion was not significantly different between those exposed to chemotherapy (37%; 95% CI 20–54%) and those unexposed (39%; 95% CI 19–59%). Similarly, the mean duration of patency was not shortened by chemotherapy (105 days in the chemotherapy group versus 119 days in the non-chemotherapy group; $P = 0.97$, Mann–Whitney U-test). We conclude that there is no evidence of increased rate of bile duct-related complications in patients receiving chemotherapy. In particular, we find no indication for the use of prophylactic antibiotics.

Key words: biliary stents, chemotherapy, pancreatic cancer

Eur J Cancer, Vol. 33, No. 2, pp. 209–213, 1997

INTRODUCTION

MALIGNANT OBSTRUCTION of the biliary tree by adenocarcinoma arising in the head of the pancreas, gall bladder or bile ducts results in jaundice, pruritis and weight loss secondary to malabsorption. If unrelieved, progressive hepatocellular and renal dysfunction will ensue. Excellent palliation can be achieved by placement of a biliary stent across the obstruction either percutaneously or endoscopically. These approaches avoid prolonged hospital admissions and the surgical morbidity and mortality associated with biliary bypass surgery [1]. However, this advantage is diminished if there is a high incidence of stent blockage, infection or gastric outflow obstruction requiring further intervention and hospitalisation.

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Received 3 Apr. 1996; revised 5 Jul. 1996; accepted 29 Aug. 1996.

The incidence of stent occlusion appears to be related to stent material and size as well as constituents of the bile which can promote sludge formation [2, 3]. The formation of sludge within polyethylene stents may be secondary to interaction between the stent and proteins derived from enterobacteria present in the bile. The resulting biofilm entraps bile salts and bacterial debris. Straight non-expanding polyethylene stents of between 10 and 12 French gauge are associated with a short duration of patency with up to 30% occlusion rate within the first 3 months [4].

To reduce clogging, patients can receive antibiotics and choleretic agents such as ursodeoxycholic acid at the time of stent insertion [5]. Administration of aspirin or tetracycline reduces formation of sludge [6], and norfloxacin with ursodeoxycholic acid at the time of stent insertion has been demonstrated to increase the duration of potency [7]. The use of cytotoxic chemotherapy to treat the underlying malig-

nancy may induce recurrent periods of neutropenia which could promote bacterial overgrowth and sludge formation. Thus, patients with malignant biliary obstruction relieved by stent may suffer with an increased rate of bile duct stent complications while receiving chemotherapy. In previously published reports of the use of bile duct prostheses for palliation of obstructive jaundice, no comment on the effect of other treatment modalities, particularly chemotherapy, has been made.

We, therefore, carried out a retrospective analysis of all patients with malignant biliary disease referred to the oncology department to determine whether patients with stents who also received chemotherapy had an increased rate of complications. We compared the infection rate, the stent occlusion rate and duration of stent patency in patients who did and did not receive chemotherapy to determine whether chemotherapy altered any of these parameters.

PATIENTS AND METHODS

Patients

A total of 83 patients with a histologically proven diagnosis of adenocarcinoma arising from the pancreas, gall bladder or biliary tree were referred to the joint Departments of Medical Oncology and Radiotherapy between 1 January 1991 and 31 December 1994. Treatment records were available for 80 patients and follow-up data were complete in 78 cases. 47 (59%) patients were referred having had a stent inserted for relief of obstructive jaundice at presentation. This group was defined as the 'primary stent group'. The remaining 33 patients referred without a stent were defined as the 'no stent group' (2 were lost to follow-up), and of these, 7 had been treated by surgical bypass. 4 patients within the no stent group developed biliary obstruction during follow-up necessitating insertion of a bile duct stent in 3 (2 Wallstents and 1 polyethylene stent) and a surgical bypass in 1 case. Any stent insertion required for relief of obstructive jaundice in either group after referral was classed as a secondary stent insertion.

The majority of patients (80%) had their primary stents inserted at St George's Hospial, London. Eighty-three percent (39/47) of stents were inserted endoscopically and were polyethylene stents, median size 10 Fg (range of gauge from 8 to 11.5 Fg). 8 patients (17%) had distensible metal stents fitted by percutaneous transhepatic cholangiogram (PTC). The protocol for endoscopic retrograde pancreatocholangiogram (ERCP) included the use of antibiotics (cefuroxime, gentamicin and metronidazole followed by 7 days co-trimoxazole).

All patients were offered therapeutic options which included best supportive care with or without chemotherapy, or radiotherapy for pain relief. Of the 53 patients who chose to have chemotherapy, the regimen used in 49 (92%) of the cases was ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, given every 21 days with continuous infusion 5-fluorouracil administered via Hickman line). Our experience with this regime in pancreatic cancer has been reported [8]. Of the 4 patients who did not receive ECF, one was treated with continuous infusion 5-FU alone, two with 5-FU and cisplatin and one with epirubicin alone. The proportion of patients who received chemotherapy with a stent *in situ* was 64% (30/47) compared to 70% (23/33) of the no stent group (Table 1).

Methods

The following parameters were compared between those fitted with a biliary stent and those in the no stent group for all patients who received chemotherapy: (a) the total number of grade 3 or 4 neutropenic episodes (absolute neutrophil count $<1.0 \times 10^9$/l); (b) all episodes of febrile illness; and (c) any clinical or biochemical evidence of cholestasis.

Table 1. Patient characteristics for primary stent and non-stent patient groups

	Primary stent *n* (%)	No stent *n* (%)	Total *n* (%)
Sex			
M	29	17	46
F	18	16	34
Age			
Mean (range)	63.6 (39–85)	59.6 (44–79)	62.1 (39–85)
Tumour type			
Cholangiocarcinoma	7	1	8
Gall bladder	3	1	4
Pancreas	37	31	68
Metastatic	17	13	30
Treatment			
Chemotherapy	30 (64%)	23 (70%)	53 (66%)
Radiotherapy	8 (17.0%)	3 (9%)	11 (14%)
Supportive care only	9 (19%)	7 (21%)	16 (20%)
Courses of chemotherapy			
6	18 (60%)	6 (26%)	24 (45%)
5	3 (10%)	–	3 (6%)
4	4 (13%)	1 (4%)	5 (9%)
3	3 (10%)	6 (26%)	9 (17%)
2	–	5 (22%)	5 (9%)
1	27 (%)	5 (22%)	7 (13%)
(Total courses)	(150)	(73)	(223)
Complications			
Grade 3 and 4 neutropenic episodes	8 (5%) in 6 patients	5 (7%) in 4 patients	13 (6%) in 10 patients

Within the primary and secondary stent groups, data regarding rate of biliary stent blockage were collected. The period of time during which chemotherapy may have a direct effect on stent occlusion rate was taken from the start of treatment to 6 weeks after the last course of chemotherapy. Duration of stent patency was taken from the date of insertion to date of removal of blocked stent or to the date of death. The proportion of patients who developed a blocked stent during the chemotherapy period was compared with those patients treated with best supportive care. The Mann–Whitney *U*-test was used to compare the difference in mean time to blockage between patients receiving chemotherapy and best supportive care. This difference was also analysed using the log-rank test to compare the median duration of patency.

RESULTS

The patient characteristics are summarised in Table 1.

What was the complication rate from stent insertion?

There were a total of 119 attempts at stent insertion of which over 75% were successful. 63% (75) of attempts were made by ERCP (endoscopic retrograde cholangiopancreatography) and 37% (44) by PTC (percutaneous transhepatic cholangiography). The failure rate with each approach was similar, 24% and 23%, respectively. The risk of cholangitis following either procedure was 8% (9/119) with two cases requiring transfer to ITU for inotropic support. The 30 day mortality following stent insertion both endoscopically and via the percutaneous route was 9% (11/119; 5 in primary stents and 6 in secondary stents) in all cases, this was associated with persistent or recurrent jaundice thought to be due to progressive disease. Two deaths occurred when replacement of stent was not possible before onset of hepato-renal failure. There were 11 episodes of biliary infection not associated with chemotherapy (3 post PTC), of which one was fatal.

The infective complication rate associated with chemotherapy

A total of 30 patients with stents *in situ* received chemotherapy. During treatment, there were eight documented episodes of grade 3 or 4 neutropenia, two of which were associated with fever (5% of all chemotherapy cycles) (Table 1). In addition, 8 patients suffered a total of 18 infective episodes not associated with a low white count (12% (18/150 cycles) rate of infection). The source of infection was unknown on two occasions and thought to arise from the chest (2 patients), urine (2 patients), shingles (1 patient), Hickman line (3 patients) and the stent in 8 cases. On only three occasions was there evidence of cholestasis with a raised bilirubin. The stent was changed in two cases, and flushed in the third (metal Wallstent).

23 patients without stents received chemotherapy. The rate of infective complications in the no stent group was similar. There were five episodes of neutropenia (7% of all chemotherapy cycles); 3 with sepsis (Table 1), and 10 infective episodes (14% (5/73 cycles) rate of infection) with a normal white cell count. The site of infection was diagnosed as the chest (2 patients), Hickman line (1 patient) and unknown in the remaining cases. Thus, the infection rate was not increased in the presence of a bile duct stent.

Blocked stents in patients receiving chemotherapy

5 patients developed recurrent obstructive jaundice secondary to blocked stent necessitating a change of stent during administration of chemotherapy. This was not associated with evidence of neutropenia or ascending cholangitis. 2 patients had carcinoma of the pancreas and 3 carcinoma of the gall bladder. A further 6 patients required a change of stent within 6 weeks of completion of chemotherapy. Thus, the total occlusion rate for the primary stent group who received chemotherapy was 37% (95% CI 20–54%). None of the 3 patients who had stents fitted after referral had a blockage whilst receiving chemotherapy.

A similar rate, 39% (9/23; 95% CI 19–59%) of stent blockage was seen in patients who were not exposed to chemotherapy (those not treated with chemotherapy or in whom the stent occluded prior to chemotherapy or greater than 6 weeks after chemotherapy). Similarly, no difference in time to change of primary stent was detected between these two groups of patients where the mean duration of patency was 105 days and 119 days for chemotherapy and non-chemotherapy groups, respectively ($P = 0.97$, Mann–Whitney *U*-test). If patients were divided into those ever exposed to chemotherapy or never then there was trend to a longer mean duration of patency in the treated group, 209 days and 131 days respectively, but this was not significant ($P = 0.477$, Mann–Whitney *U*-test) and most likely reflects the shorter survival in the non-chemotherapy group. The median duration of patency for all stents (primary and secondary) was 72 days for the non-chemotherapy group compared with 76 days for the chemotherapy treated group ($P = 0.44$, log-rank test).

DISCUSSION

A diagnosis of adenocarcinoma of the pancreas carries a very poor prognosis and palliation of symptoms is the most important aim of management. The use of biliary stents for the relief of obstructive jaundice allows patients to sustain a relatively asymptomatic life style avoiding debilitating pruritis, steatorrhea and the risk of renal failure. One of the main drawbacks of polyethylene stents is their relatively short lifespan. The median duration of patency is reported to be between 120 and 190 days [9–12] but the occlusion rate may be as low as 10.8% at 6 months [13]. In the event of recurrent obstructive jaundice, the stent needs to be replaced which is associated with a further inpatient stay and invasive procedure.

The main cause of blockage is sludge forming within the stent. This may be promoted by an overgrowth of enterobacteria within the biofilm that forms along the inside of the stent. The more expensive expandable metal stents are less likely to block as they form a wider channel, expanding *in situ* to a diameter of 1 cm (equivalent to 30 Fg), and have less area for protein adhesion. Direct comparisons between the two types of stent have shown a longer duration of patency for metal stents with occlusion rates of 22% versus 43% [14] and 18% versus 50% [10], and studies of long-term follow-up have reported a median duration of metal stent patency of 8.2 months with a 46.2% occlusion rate [15], and 39.9 weeks with a occlusion rate of 35% [16]. Blockage was caused by tumour ingrowth through the mesh of the stent. This compares with approximately 200 days (17 weeks) median duration of patency for a size 12 and 10

Fg plastic prosthesis [13, 17]. However, this advantage needs to be balanced against the extra cost and absolute requirement for a long duration of patency in a situation where the prognosis of patients is limited to a few months. It is not clear whether the avoidance of further intervention by fitting an expensive primary metal stent represents a significant cost benefit [9, 10, 14]. In general, polyethylene stents are adequate for the majority of patients with malignant obstructive jaundice and metal stents should be reserved for those with a longer prognosis [11].

One exception could be that if patients are to receive chemotherapy, there is a theoretical risk of accentuating sludge formation and shortening the lifespan of stents. Thus, any advantage from chemotherapy may be negated by the need for further admissions for a change of stent. We set out to determine whether patients with a diagnosis of pancreatic carcinoma or associated malignancies who had required a stent for the relief of obstructive jaundice suffered increased stent-related complications if they also received chemotherapy and were at risk of neutropenic sepsis.

Within our patient population, the majority had a stent *in situ* at the time of referral and over 50% proceeded to chemotherapy. Within the chemotherapy group, we had similar proportions of patients with and without stents. The complications associated with stent insertion were cholangitis (8%) with a 30-day mortality rate of 9%. These results are similar to those reported by Davids and colleagues and Knyrim and colleagues who reported a complication rate of 11–22% and 30-day mortality of 4–14% [9, 14].

Comparison of the infective complications associated with chemotherapy between those with and without a stent showed that both the rate of neutropenia (5% versus 7% per chemotherapy cycle) and sepsis (12% versus 14%) were similar implying there was no particular increased risk of infection from the stent itself. In only 3 patients was there any rise in bilirubin with alkaline phosphatase. Comparison of cholestatic episodes between the two groups was not valid as patients without jaundice at presentation are likely to have cancer within the body or the tail of the pancreas and are at a lower risk of obstructive jaundice.

The mean duration of primary stent patency (105 days, chemotherapy group and 119 days, non-chemotherapy group) was similar to that reported elsewhere [9–12]. The median duration of patency for all stents (i.e. combining primary and secondary stent groups) was considerably lower reflecting the shorter duration of patency for secondary stents and the poor survival rate of this group of patients. The rate of stent occlusion in patients receiving chemotherapy and in the 6 weeks following compared to those before or greater than 6 weeks after chemotherapy were not significantly different. The arbitrary choice of 6 weeks after chemotherapy was used as it was assumed that any interaction between chemotherapy and stent blockage would be related to bacterial overgrowth during periods of neutropenia. When the duration of primary stent patency was compared between those ever or never exposed to chemotherapy there was no significant difference for the chemotherapy group. It would appear that patients who require biliary stenting to relieve obstructive jaundice secondary to malignant stricture do not have a shorter period of benefit from the stent or an increase in infective complications if they also have chemotherapy.

Although our patients represent a heterogeneous group, the majority were fitted with polyethylene prostheses and received prophylactic antibiotics at the time of stent insertion. The number of patients with expandable metal stents was too small to detect any advantage using this form of stent in patients receiving chemotherapy. However, other authors have shown a cost benefit in terms of avoiding further intervention by using primary metal stents in patients likely to have a good prognosis [9, 10, 14].

In summary, in our experience of bile duct stent complications in patients receiving chemotherapy, we did not detect a significant increase in rate of stent blockage, shortening of duration of stent patency, or infection. We would, therefore, not advocate that any special precautions are taken in the administration of chemotherapy to patients with adenocarcinomas arising in the pancreas or biliary tree who have had a biliary stent inserted to relieve obstructive jaundice. In particular, we find no indication for the use of prophylactic antibiotics.

1. Shepard HA, Royle G, Ross APR, Diba A, Arthur M, Colin-Jones D. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomised trial. *Br J Surg* 1988, **75**, 1166–1168.
2. Coene PPLO, Groen AK, Cheng J, Out MMT, Tytgat GNJ, Huibregtse K. Clogging of biliary endoprosthesis: a new perspective. *Gut* 1990, **31**, 913–917.
3. Leung JWC, Ling TKW, Kung JLS, Vallance-Owen J. The role of bacteria in the blockage of biliary stents. *Gastrointest Endosc* 1988, **34**, 19–22.
4. Huibregtse K, Katon RM, Coene PP, Tytgat GNJ. Endoscopic palliative treatment in pancreative cancer. *Gastrointest Endosc* 1986, **32**, 334–338.
5. Reichen J. Pharmacologic treatment of cholestasis. *Semin Liver Dis* 1993, **13**, 302–315.
6. Smit JM, Out MMJ, Groen AK, *et al.* A placebo controlled study on the efficiency of aspirin and deoxycycline in preventing clogging of biliary endoprostheses. *Gastrointest Endosc* 1989, **35**, 485–489.
7. Barrioz T, Ingrand P, Besson L, de Ledinghen V, Silvain C, Beauchant M. Randomised trial of prevention of biliary stent occlusion by ursodeoxycholic acid plus norfloxacin. *Lancet* 1994, **344**, 581–582.
8. Evans TRJ, Lofts FJ, Mansi JL, Glees JP, Knight MJ, Dalgleish AG. A phase II study of continuous infusion 5-fluorouracil with cisplatin and epirubicin in inoperable pancreatic cancer. *Br J Cancer* 1996, **73**, 1260–1264.
9. Davids PHP, Groen AK, Rauws EAJ, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992, **340**, 1488–1492.
10. Wagner H, Knyrim K, Vakil N, Klose KJ. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. *Endoscopy* 1993, **25**, 213–218.
11. Siegel JH, Pullano W, Kodsi B, Cooperman A, Ramsey W. Optimal palliation of malignant bile duct obstruction: experience with endoscopic 12 French prostheses. *Endoscopy* 1988, **20**, 137–141.
12. Matsuda Y, Shimakura K, Akamatsu T. Factors affecting the patency of stents in malignant biliary obstructive disease: univariate and multivariate analysis. *Am J Gastroenterology* 1991, **86**, 843–849.
13. Frankes JT, Johanson JF, Stake JJ. Optimal timing for stent replacement in malignant biliary tract obstruction. *Gastrointest Endosc* 1993, **39**, 164–167.

14. Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993, **25**, 207–212.
15. O'Brien S, Hatfield ARW, Craig PI, Williams SP. A three year follow up of self expanding metal stents in the endoscopic palliation of long term survivors with malignant biliary obstruction. *Gut* 1995, **36**, 618–621.
16. Mathieson JR, McLoughlin RF, Cooperberg PL, *et al.* Malignant obstruction of the common bile duct: long-term results of Gianturco–Rosch metal stents used as initial treatment. *Radiology* 1994, **192**, 663–667.
17. Speer AG, Cotton PB, Russel RC, *et al.* Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987, **ii**, 57–62.