An Italian study on treatment trends and outcomes of patients with stage III pancreatic adenocarcinoma in the gemcitabine era: is it time to change?

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A series of 650 patients treated between 1997 and 2007 at 10 Italian centers was analyzed to assess treatment trends and efficacy in stage III pancreatic adenocarcinoma. Data on patient characteristics, treatment and outcomes were collected. The inclusion criteria were pathological diagnosis of stage III pancreatic adenocarcinoma; age more than 18 years, Eastern Cooperative Oncology Group performance status less than 3, and no past therapy. Most patients (95%) received upfront chemotherapy, which mainly consisted of gemcitabine alone (*N*=323), gemcitabine-based four-drug combinations (*N*=107), gemcitabine-platinum compound doublets (*N*=87), or intra-arterial gemcitabine-free triplets (*N*=57). The use of gemcitabine–platinum compound doublets increased over time (1997–2001: 2%; 2002–2007: 21%) whereas an inverse trend was observed for gemcitabine (71–61%). No overall survival (OS) difference was observed between patients enrolled in clinical trials and those not enrolled. The median and 1-year OS were 9.5 months and 35.5% for patients treated with gemcitabine; 8.9 months and 36.8% for those treated with gemcitabine-free intra-arterial triplets; 13.3 months and 55.8% for those treated with gemcitabine-platinating agent doublets; and 16.2 months and 62.6% for those treated with gemcitabine-based four-drug combinations. Moreover, the median and 1-year OS were 12.7 months and 51.4% in patients who underwent planned consolidation chemoradiation, and 8.4 months and 30.4% in patients who did not. The use of a strategy consisting of a gemcitabine-platinating agent containing chemotherapy followed by consolidation chemoradiation has been increasing over time and may represent a suitable choice in the therapeutic management of stage III pancreatic adenocarcinoma. *Anti-Cancer Drugs* 21:459–464 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Pancreatic cancer is the eleventh most common cancer and the fourth leading cause of cancer mortality in the Western world [1]. Despite advances in our understanding of the molecular and genetic basis of this disease, little improvement in outcome has been achieved through surgical procedures, radiotherapy techniques and chemotherapy. Approximately 80–85% of patients have unresectable disease at the time of diagnosis owing to the presence of distant metastases (stage IV) or to the involvement of the regional main vessels (stage III) [2]. The median survival for patients with stage III disease is in the range of 6–12 months [3–8] and systemic dissemination affects 66–74% of patients [9–12]. The optimal therapeutic management of stage III disease remains controversial mostly because of the limited number of stage-specific randomized trials testing the role and timing of chemotherapy and chemoradiation. Chemoradiation has been shown to be superior to radiotherapy alone [3,4,13]. Conversely, comparison of chemoradiation and chemotherapy has produced conflicting results [5–8,13]. It should be taken into account that older studies used outdated radiation techniques and that more recent trials were prematurely completed owing to poor accrual. In all these trials, the sample size was limited to fewer than 120 patients, leading to data with wide confidence intervals. Accordingly, it seems challenging to draw firm conclusions and to outline stage-specific guidelines for ordinary clinical practice.

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This study focused on the treatment and outcomes of patients receiving an upfront therapy for stage III unresectable ductal pancreatic carcinoma. The aims of the study were (i) to estimate treatment trends, (ii) to compare the outcomes of different chemotherapy regimens and (iii) to assess whether the outcomes of patients managed in the clinical practice could differ from those of those enrolled in clinical trials.

Materials and methods

Participating institutions

Ten institutions were involved in this study: one oncology department administering four-drug gemcitabine–platinum–fluoropyrimidine-based regimens [14–18] (institute 1); one oncology department administering intra-arterial chemotherapy with gemcitabine-free three-drug combination [19] (institute 2); one national referral center for pancreatic surgery (institute 3) that, after diagnosis, referred patients to oncology departments spread all over Italy; and seven oncology departments located in seven different Italian regions (institutes 4–10).

Study group

The inclusion criteria were pathological diagnosis of stage III unresectable pancreatic adenocarcinoma performed between January 1997 and December 2007, age more than 18 years, Eastern Cooperative Oncology Group performance status (PS) less than 3, and no past chemotherapy or radiotherapy. The staging workup was similar across institutions, and included a complete history and physical examination; blood analysis (complete blood cell count, liver and kidney function tests); carcinoembryonic antigen and cancer antigen 19-9 levels; and a total body computed tomography (CT) scan or magnetic resonance imaging in patients who were allergic to CT contrast liquid. Endoscopic ultrasound assessment was performed in selected cases. Laparoscopy was not included in the staging workup. Patients with Vater's ampulloma or adenocarcinoma of the biliary tract were not eligible. Data on patient characteristics, diagnosis, treatment, objective response, and survival were provided by each institution.

Statistical considerations

The clinical characteristics of the therapeutic subgroups were compared using the χ^2 test or Fisher's exact test for categorical variables as appropriate according to the sample size. Survival curves were estimated with the Kaplan–Meier method. OS was calculated from the date of treatment start to death or the last date of follow-up. Owing to the difference in timing of radiological assessment during treatment and follow-up across institutions, data on progression-free survival were not analyzed. As the evaluation of radiological responses, even with newer imaging techniques, is considered rather unreliable owing to the vigorous desmoplastic reaction including inflammation and fibrosis within and around the tumor [20], objective response to treatment was not analyzed. As a variety of regimens were administered across institutions and as there are too many unquantifiable variables that might explain a different outcome, OS data were only analyzed using descriptive statistics. Analyses were carried out using the Statistica 4.0 statistical package for Windows (1993; Statsoft, Tulsa, Oklahoma, USA).

Role of the funding source

No funding sources supported the design of the study; the collection, analysis, or interpretation of the data; or the writing of the report or the decision to publish the results.

Results

Study population

Six hundred and fifty patients were included in the study. The characteristics of the population and of the groups of patients, defined on the basis of accrual in clinical trials, are shown in Table 1. The group of patients with unknown trial status (corresponding to the group of patients from institution 3) included a significantly higher percentage of patients with PS 2 than the other two groups.

Institutions 1 and 2 may be considered less representative of national trend to enrol patients in a trial owing to the particular chemotherapy combinations used. Furthermore, data on trial status were not provided by institution 3. Thus, the national trend may be better estimated by limiting observation to institutions 4–10, which included 42 of 150 patients (28%) in clinical trials.

The characteristics of the groups of patients defined on the basis of referral institution are shown in Table 2.

Table 1 Patient characteristics at baseline

	Total (%)			
Characteristic	All patients	Enrolled in a trial	Not enrolled	Unknown
Patients	650	191	124	335
Median age	63	63	64	63
ECOG PS				
0	171 (26)	67 (35)	60 (48)	44 (13)
1	367 (57)	110 (58)	30 (24)	227 (68)
2	72 (11)	8 (4)	1 (1)	63 (19)
Unknown	40 (6)	6 (3)	33 (27)	1 (0)
CA19.9				
Median U/ml	284	348	277	274
<ULN	135 (21)	37 (19)	25 (20)	73 (22)
>ULN	319 (49)	96 (50)	52 (42)	171 (51)
<median				
>Median	162 (25)	45 (24)	35 (28)	82 (25)
Unknown	34 (5)	13 (7)	12 (10)	9 (3)
Year				
1997–2001	260 (40)	69 (36)	25 (20)	166 (50)
2002–2007	390 (60)	122 (64)	99 (80)	169 (50)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ULN, upper limit of laboratory normal value.

Table 2 Patient characteristics per institution at baseline

Characteristic	Total (%)			
	Institution 1	Institution 2	Institution 3	Institutions 4–10
Patients	108	57	335	150
Median age (years)	62	61	63	64
ECOG PS				
0	48 (44)	16 (28)	44 (13)	63 (42)
1	53 (49)	41 (72)	227 (68)	46 (31)
2	5 (5)	0 (0)	63 (19)	4 (3)
Unknown	2 (2)	0 (0)	1 (0)	37 (25)
CA19.9				
Median U/ml	279	306	274	311
<ULN	20 (19)	12 (21)	73 (22)	30 (20)
>ULN <median	61 (56)	24 (42)	171 (51)	63 (42)
>Median	26 (24)	11 (19)	82 (25)	43 (29)
Unknown	1 (1)	10 (18)	9 (3)	14 (9)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ULN, upper limit of laboratory normal value.

Table 3 Patient characteristics per treatment arm at baseline

Characteristic	Total (%)			
	G	G-P/O	FLEC	PEFG/PEXG/PDXG
Patients	323	87	57	107
Median age	66	66	61	62
ECOG PS				
0	68 (21)	23 (26)	16 (28)	52 (49)
1	189 (58)	53 (61)	41 (72)	47 (44)
2	51 (16)	7 (8)	0 (0)	4 (4)
Unknown	15 (5)	4 (5)	0 (0)	4 (4)
CA19.9				
Median U/ml	300	287	306	348
<ULN	69 (21)	16 (18)	12 (21)	19 (18)
>ULN <median	158 (49)	37 (42)	24 (42)	60 (56)
>Median	84 (26)	23 (27)	11 (19)	27 (25)
Unknown	12 (4)	11 (13)	10 (18)	1 (1)
Trial statusenrolled	36 (11)	11 (13)	57 (100)	87 (81)
Not enrolled	47 (15)	38 (44)	0 (0)	20 (19)
Unknown	240 (75)	38 (44)	0 (0)	0 (0)

C, carboplatin; D, docetaxel; E, epirubicin; ECOG, Eastern Cooperative Oncology Group; F, 5-fluorouracil; G, gemcitabine; L, levofolinic acid; O, oxaliplatin; P, cisplatin; PS, performance status; ULN, upper limit of laboratory normal value; X, capecitabine.

As mentioned above, the PS profile was significantly worse in institution 3. No other significant difference was observed across groups.

Treatment and treatment trends

According to the eligibility criteria, all the patients received active treatment for their disease, which was heterogeneous across institutions and over time. Upfront chemotherapy was administered to 615 patients (95%) and upfront chemoradiation to 35 patients (5%). Only those treatment groups that included more than 50 patients each were considered for comparative outcome analysis, to obtain sufficient statistical consistency. Overall, 574 of 650 patients (88%) received one of the following therapies: (i) single-agent gemcitabine; (ii) gemcitabine plus platinating agent doublets; (iii) gemcitabine-free three-drug intra-arterial combination; or (iv) four-drug gemcitabine–cisplatin–fluoropyrimidine-based combinations (Table 3). Consolidation chemoradiation after upfront chemotherapy was part of treatment policy in six of nine oncology departments, while the intention to use chemoradiation was unknown for patients included by institution 3. Altogether, 222 patients (74%) were included by followers of chemoradiation, while 79 patients were included by not followers.

The group of patients treated with gemcitabine alone included a significantly larger number of patients with PS 2 (16%) when compared with three or four-drug combinations (0 and 4%, respectively). More patients treated with gemcitabine–platinating agent doublets had PS 2 (8%) with respect to three-drug intra-arterial chemotherapy. No other significant difference was observed across groups, apart from rates of accrual in clinical trials, which were significantly higher in institutions 1 and 2.

Single-agent gemcitabine was the therapy most often used both between 1997 and 2001 and between 2002 and 2007 (55 and 46% of cases, respectively). When only institutions 3–10, which were more representative of national trends, were considered, 71 and 61% of patients received single-agent gemcitabine during the two time intervals. Between time intervals, the use of gemcitabine-fluoropyrimidine doublets decreased from 5 to 1% of cases (from 7 to 1% in institutions 3–10), the use of upfront chemoradiation decreased from 8 to 3% (from 11 to 5% in institutions 3–10) and the administration of gemcitabine-platinating agent doublets increased from 2 to 21% (from 3 to 28% in institutions 3–10). Four-drug chemotherapy [14–18] was rarely used, apart from at institution 1 (2%), while three-drug intra-arterial chemotherapy [19] use was confined to institution 2.

Treatment outcome

Final analysis was performed on 28 March 2009 when 616 (95%) of the 650 patients had died and 34 of the surviving patients had completed at least 12 months of follow-up (median follow-up 19 months, range 12–51 months). The median and actuarial 1-year OS for the whole group were 10.9 months and 43%, respectively.

Chemotherapy outcome

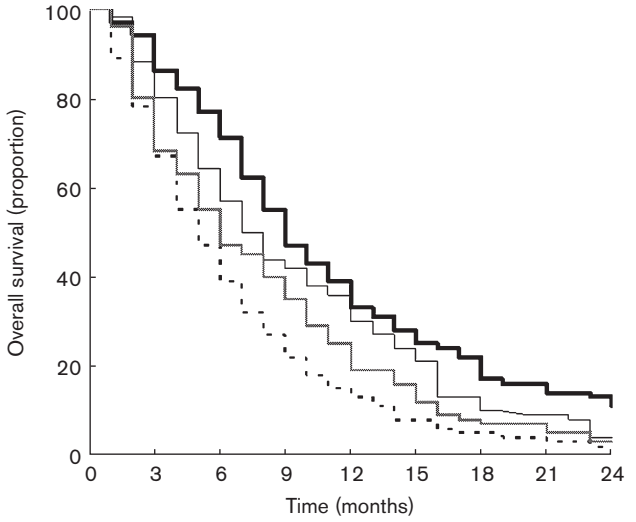
OS figures and curves based on chemotherapy regimen are reported in Table 4 and in Fig. 1.

Table 4 Efficacy analyses summary

Overall survival	G	G-free triplets	G+P	4D regimens
Median (months)	9.5	8.9	13.3	16.2
Interquartile range	5.7–14.2	6.2–14.8	8.3–19.0	9.4–22.4
1-year (%)	35.5	36.8	55.8	62.6
95% CI	30.5–40.5	24.0–49.6	45.1–66.5	53.3–71.9
2-year (%)	7.8	8.8	11.9	22.7
95% CI	4.4–11.2	1.3–16.3	4.4–19.4	14.5–30.9

CI, confidence interval; D, drugs; G, gemcitabine; P, platinating agent.

Fig. 1



Overall survival on the basis of treatment regimen. Four-drug regimens ——: gemcitabine–platinating agent doublets ——: gemcitabine - - - -: intra-arterial gemcitabine-free triplets ——.

As reported above, the PS profiles of patients included by institution 3 were worse than those of patients from other institutions. To limit the risk of a selection bias, survival figures based on administered treatment after excluding patients from institution 3 were also evaluated. The median and 1-year OS were 9.8 months [interquartile range (IQR): 6.8–14.2] and 34.9% [95% confidence interval (CI): 24.5–45.3%] for patients treated with gemcitabine; 11.5 months (IQR: 5.9–17.9) and 44.9% (95% CI: 30.7–59.1%) for those treated with gemcitabine-platinating agent doublets; and remained unmodified for gemcitabine-free triplets and for gemcitabine-based four-drug combinations.

When only patients with PS = 0 or PS = 1 were included in the analysis, the median and 1-year OS were 9.7 months (IQR: 6.0–14.4) and 35.9% (95% CI: 30.1–41.7%) for patients treated with gemcitabine; 13.4 months (IQR: 8.4–19.1) and 58.3% (95% CI: 47.2–69.4%) for those treated with gemcitabine–platinating agent doublets; 16.2 months (IQR: 9.8–22.1) and 63.1% (95% CI: 53.6–72.6%) for those treated with gemcitabine-based four-drug combinations; and remained unmodified for those treated with gemcitabine-free triplets.

It is worthy of note that the survival curves of patients enrolled in clinical trials were similar to those of those patients not enrolled, and this similarity was confirmed regardless of the type of treatment the patients had received (data not shown).

Consolidation chemoradiation

Consolidation chemoradiation was planned for 222 of the 301 patients for whom intention to treat was known. The median and 1-year OS were 12.7 months (IQR: 8.0–19.6) and 51.4% (95% CI: 44.7–58.1%) in these patients; and 8.4 months (IQR: 6.2–13.7) and 30.4% (95% CI: 20.1–40.7%) in 79 patients who did not undergo planned chemoradiation. Past chemotherapy was heterogeneous in the two groups. In fact, among the 79 patients who did not undergo planned chemoradiation, 57 (72%; median OS 8.9 months) had received past gemcitabine-free intra-arterial chemotherapy, 20 (25%; median OS 8.8 months) with gemcitabine and two with other regimens. Among the 222 patients with planned chemoradiation, 107 (48%; median OS 15.4 months) were treated with four-drug regimens, 63 (28%; median OS 10.9 months) with gemcitabine, 49 (22%; median OS 11.5 months) with gemcitabine-platinating agent doublets, and 3 with other regimens.

Chemoradiation was administered to 116 of 222 patients (52%): 19 of 63 (30%) previously treated with gemcitabine, 25 of 49 (51%) previously treated with gemcitabine-platinating agent doublets, and 72 of 107 (67%) previously treated with four-drug regimens.

Patients undergoing resection

Overall, 20 patients (3%) were rescued to surgery with radical intent at the end of treatment. Namely, chemotherapy allowed downstaging and resection of the tumor in 14 of 107 patients (13%) treated with gemcitabine-based four-drug combinations, in 5 of 87 (6%) receiving gemcitabine-platinating agent doublets and in 1 of 323 (0.3%) treated with single-agent gemcitabine. The median and 5-year OS in these patients were 19.5 months and 9%, respectively.

Discussion

This study reports the trends in treatment choice and clinical outcomes of a large series of patients with stage III unresectable pancreatic ductal adenocarcinoma. The population included in this study reflects the typical population with locally advanced pancreatic cancer in terms of patient-related and tumor-related factors and survival figures. For patients with locoregionally advanced disease, the reported median and 1-year OS were in the range of 8–14 months and of 32–62%, respectively [8,10–12,21–23], which is comparable to the 10.9 months and 42% observed in the study population. Despite the retrospective nature of the study and the heterogeneity of the participating institutions in terms of patient selection, treatment strategies and rate of accrual in clinical trials, the information gathered provides insight into the management of this stage of disease. In fact, the lack of stage-specific completed randomized trials does not allow us to draw evidence-based guidelines for clinical practice and, from this perspective, the retrospective exploratory analysis of a large series may generate attractive hypotheses for future trials.

Whether patients with stage III pancreatic adenocarcinoma should receive chemotherapy alone, concomitant chemoradiation, or a combination of both treatments is still under debate. However, in the studied population, upfront chemotherapy was the vastly prevailing choice (95% of patients), whereas only 5% of patients were referred for upfront chemoradiation. Owing to the limited sample size of the latter group, no comparison could be made between the two strategies.

Systemic chemotherapy seems to be the most logical choice because metastatic failure affects 66–74% of patients with initial stage III disease [9–12], likely owing to the presence of radiologically undetectable microscopic distant lesions at time of diagnosis. Induction chemotherapy is the preferred option because it may eradicate micrometastatic disease, select a subgroup of patients without early metastatic course who are most likely to benefit from locoregional therapy, or even shrink the tumor, thus increasing the probability of responding to subsequent chemoradiation.

The optimal duration of induction chemotherapy has not been clearly established [22], and no useful information to foster the debate can be obtained from this study.

An optimal chemotherapy regimen is also being discussed. In institutions that are representative of national treatment trends, single-agent gemcitabine remains the foremost choice. However, its use decreased over time (from 71 to 61%) whereas an increasing proportion of patients (from 3 to 28%) received gemcitabine-platinating agent doublets, likely owing to an over-emphasized PFS advantage and despite the lack of any significant improvement in OS [24–27]. The current study was not designed to substitute a randomized trial and the results should be taken into account with caution. Subgroup analyses on the basis of PS and multivariate analysis stratifying by main prognostic factors seem to endorse the consistency of results and suggest that gemcitabine-platinating agent-based combination chemotherapy may improve OS over single-agent gemcitabine. From the same perspective, the study also suggests that four-drug regimens [14–18] yield better results than other chemotherapy combinations. In contrast, gemcitabine-free intra-arterial triplets [19] do not seem to improve OS with respect to single-agent gemcitabine, and seem to be inferior to gemcitabine-based combinations.

Consolidation chemoradiation was advocated as a beneficial approach to improving survival in patients whose disease had not progressed during upfront chemotherapy compared with continuation of the same chemotherapy [23]. Approximately 50% of patients in this study received the planned chemoradiaton regimen, which was comparable to 50–74% in other series [9–12,28,29]. The observed survival figures seem to support the use of chemoradiation as a consolidation strategy, as the intent to administer it was associated with median survival prolongation from 8.4 to 12.7 months. Again, the results of this analysis should be interpreted with caution owing to the heterogeneity of induction chemotherapy in the two groups. In the subgroup of patients receiving gemcitabine alone, consolidation chemoradiation yielded an improvement in OS of approximately two months. However, the number of patients for this analysis was limited ($N = 63$ vs. 20). Accordingly, it is impossible to exclude the fact that the difference between survival curves was related to past chemotherapy regimen rather than to consolidation chemoradiation. The potential benefit of consolidation chemoradiation deserves prospective randomized validation. This issue is currently being addressed in an ongoing randomized phase III trial conducted by the GERCOR and Arbeitsgemeinschaft Internisttische Onkologie groups [23].

Although not intended as a typical conversion treatment, highly active chemotherapy regimens may eventually shrink bulky tumors and through radical surgery cure a small number of patients with initial unresectable stage III disease. In this study, tumor resection after induction chemotherapy was performed in 3% of patients, with remarkable differences across treatment arms, ranging from 0.3% of patients treated with single-agent gemcitabine to 13% of those receiving four-drug regimens. However, the assessment of resectability is dependent on the experience, confidence, and motivation of each surgical team [30]. Accordingly, the multicentre nature of the study may raise some concerns about the homogeneity of surgical resectability assessment, and the results must be taken viewed with caution.

Overall, the survival figures of patients with stage III disease remain disappointing. From this perspective, the rate of patients who were enrolled in clinical trials (28%), although remarkable, is nevertheless unsatisfactory, and a greater commitment towards outcome improvement is warranted. Another remarkable finding of this study was the comparable patient outcomes regardless of inclusion in a prospective trial. The reliability of these results in terms of both the quality of patient care at the involved institutions and the applicability of the results from prospective trials to the general population managed in clinical practice is reassuring.

In conclusion, there is a growing trend towards recommending upfront combination chemotherapy followed by consolidation chemoradiation. The results of this study show that this approach may represent a suitable choice in the therapeutic management of locally advanced pancreatic adenocarcinoma and that consolidation chemoradiation may offer a promising contribution to disease control. Accordingly, the roles of both combination chemotherapy and consolidation chemoradiation deserve to be confirmed by prospective trials. In addition, the

results of the current study represent an opportunity to perform prospective assessment of therapeutic strategies in stage III pancreatic cancer separately from stage IV disease, and call for a more convinced effort to include patients in clinical trials aimed to better define optimal therapeutic management, eventually improving patient outcome.

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