Systemic and Regional Chemotherapy for Advanced and Metastasized Pancreatic Cancer

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27.1 Introduction

Pancreatic cancer remains a challenge in cancer therapy. The 5-year survival rate does not exceed 5% because of late symptoms, and there are nearly as many cancer deaths as patients diagnosed each year, reflecting the poor prognosis associated with pancreatic cancer. At the time of diagnosis, only 10–15% of the patients have still limited disease and are amenable to surgical resection. Systemic chemotherapy in non-resectable tumors has been of modest benefit and most have been associated with significant toxicity.

In the last two decades numerous well-designed randomized phase III studies have been performed in order to elucidate the optimal treatment strategy for advanced or metastasized pancreatic cancer. Although they appeared to offer much hope in treating this disease, the outcome has been very limited. Induction chemotherapy for locally advanced or metastasized tumors is the predominant indication in most diagnosed pancreatic cancers. Since, at diagnosis, life expectancy was about 2–4 months, Burris' study with gemcitabine as first-line therapy for advanced pancreatic cancer showing a significant survival advantage of 2 months was a substantial step forward [1]. Gemcitabine also improved clinical benefit response (CBR) and until now its efficiency has not been surpassed by any other single agent therapy. However, since in multiple trials single agent gemcitabine did not exceed overall survival figures of approximately 6 months, new strategies were warranted.

It was quite understandable that in view of the lack of success of other monotherapies, combination therapies were administered, hopefully to improve overall survival. A trial of

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gemcitabine combined with capecitabine versus gemcitabine alone [2, 3] resulted in a median overall survival of 7.4 months compared with 6 months for gemcitabine alone and an absolute improvement in 1-year survival of 7% (26% versus 19%). Two further trials comparing gemcitabine alone or in combination with capecitabine failed to reveal any substantial differences in efficacy between the two groups [4, 5].

Combination therapies, such as gemcitabine with 5-FU [6], cisplatin [7], irinotecan [8], oxaliplatin [9, 10], cisplatin, and 5-FU [11] or ISIS-2503 [12], have failed to show improvement. Because of negative results of randomized phase II studies of gemcitabine at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer, none of these approaches was recommended for routine use [13]. Other phase III studies have been completely negative without any suggestion of increased efficacy such as comparing 5-FU with 5-FU plus cisplatin [14], gemcitabine alone, or with cisplatin [15], 5-FU alone or with mitomycin [16], as well as the combination of gemcitabine with exatecan [17], pemetrexed [18], or the targeted agents tipifarnib [19] or marimastat [20]. Also the addition of targeted agents like bevacizumab and erlotinib to gemcitabine [21] failed to demonstrate an advantage over gemcitabine alone; likewise, the addition of bevacizumab versus placebo could not translate into an improvement in overall survival. Other antiangiogenetic agents, too, have been recently communicated to be ineffective in this setting.

In a phase III study published by Moore et al. [22] the combination of gemcitabine with the tyrosine kinase inhibitor erlotinib showed a statistically significant difference in overall survival compared with gemcitabine alone. This was the first time any drug added to gemcitabine resulted in an improvement of overall survival. In this study including 569 patients totally with locally advanced pancreatic cancer the survival advantage was 6.24 versus 5.91 months. The 1-year survival was more notable, amounting to 23% versus 17%. Analysis conducted to define the population of patients that could benefit most from this therapy revealed that the side effect “skin rash” was an indicator for response. It was also stated that females do not benefit from erlotinib compared to males.

Although the gemcitabine/erlotinib combination therapy reveals a distinct advantage in a selected group of patients, it can be stated that combination therapies have been globally disappointing. Pancreatic cancer, in general, has a propensity of being chemoresistant and dose-intense systemic chemotherapies did not overcome this resistance.

In numerous recent studies, importance was given to surrogate end points like improvement of objective response rates, decline of the tumor marker CA 19-9, or progression-free survival (PFS) which, however, turned out to have no meaningful impact on overall survival. In addition, it has been noted in most trials that patients with reduced performance status and poor prognosis do not benefit from chemotherapy for advanced disease. Reviewing the achievements in terms of survival and quality of life from therapy of pancreatic cancer, the results are poor, at high cost, financially as well as in terms of adverse effects. It has been suggested that the burden from treatment-related adverse effects should not be added to those already suffering with the disease [11]. Survival benefits of statistically significant, 2 months at the most, at the cost of side effects or unacceptable toxicity demand the development of innovative strategies with better options in the treatment of pancreatic cancer.

27.2 Approaching the Target

Studies conducted so far were based on the evaluation of the effect of various drug combinations on survival. After all it seems reasonable to shift away from studies based on trial-and-error testing [23]. Targeted agents, active theoretically and in xenograft models, might play a paramount role in the future when there is better understanding of the complex interactions of signaling pathways and their possible blockade.

In many tumor models, the increase of local drug exposure actually is an important parameter to improve clinical results [24].

As distinct from other tumors, pancreatic cancer has a characteristic that explains the reason of poor responsiveness of primary tumors as opposed to metastases. There is a high degree of fibrotic encasement in primary tumors with very restricted vasculature [25–29]. Intraoperatively primary pancreatic carcinomas appear almost avascular, whereas liver metastases of the same tumor show an excellent blood supply when patent blue is injected through the hepatic artery for staining (Fig. 27.1). In contrast, normal pancreatic tissue reveals much better staining than the primary tumor itself when patent blue is injected intra-arterially. Better response and reduction of liver metastases was reported in some intra-arterial studies [30–33]. This phenomenon was taken into account in a study mentioned previously [13], where patients who had only locally advanced disease were excluded in order to avoid confounding evaluation of response.

27.3 Intra-arterial Chemotherapy

Studies with intra-arterial chemotherapy are heterogenous and encompass the administration of various drugs in a variety of dosages and times of application [30–33]. So far, there is no uniform standard and know-how about which application is the best. However, despite the

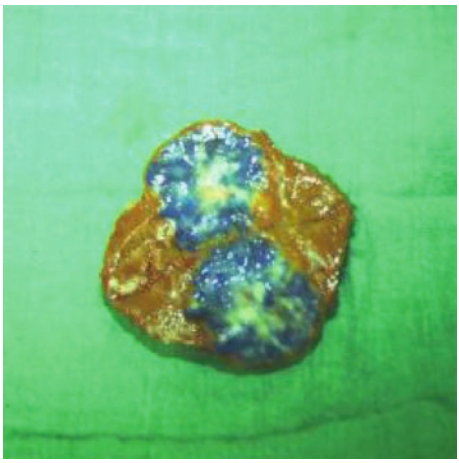

Fig. 27.1 Intra-arterial blue staining of liver metastases from pancreatic cancer. The metastases has more uptake of methylene blue than the surrounding liver parenchyma

great variety throughout all studies, survival time is generally superior and toxicity lower as compared with data from systemic chemotherapy. There are two randomized phase III trials comparing systemic versus regional chemotherapy. One study comparing intravenous application versus celiac axis infusion of the three drug combination mitomycin, mitoxantrone, and cisplatin was terminated early because of the obvious discrepancy in survival in favor of intra-arterial chemotherapy and markedly increased toxicity in the systemic arm [34]. The Italian SITILO prospective randomized phase III study was conducted with a systemic arm of standard gemcitabine and a locoregional arm with 5-fluorouracil, leucovorin, epirubicin, and carboplatin. A third arm with 5-fluorouracil and leucovorin alone given systemically was soon abandoned and the study continued with the systemic and locoregional arm [25]. This phase III study is of great interest, because the median overall survival of 5.85 months confirms the results of previous trials with gemcitabine, and on the other hand reveals a significant advantage in median overall survival of 7.9 months in the locoregional arm, where 12 months and 18 months survival are 35% and 15%, respectively. Of interest in this study is that there is more systemic toxicity in the intra-arterial arm, because of a different, non-gemcitabine containing intra-arterial drug combination, and a substantial spill of drugs in the venous drainage after the first pass through the arterial access.

27.4 Induction Chemotherapy

Induction chemotherapy for locally advanced disease is suggested to downstage the primary tumor and to achieve resectability, regardless of accompanying liver or local lymph node metastases. A tumor in the head of the pancreas itself is more life threatening than locoregional or distant metastases.

In a meta-analysis of 111 studies and 4,400 patients with primarily non-resectable or borderline resectable pancreatic cancer treated with preoperative induction radio- or chemotherapy, an estimated 33.2% resectability rate after systemic induction chemotherapy was reported [35]. A comparatively similar rate was achieved with intra-arterial microembolization with degradable starch microspheres in a phase II study on 265 cases [31]. Eighty patients had survived 1 year or more. Out of these 80 patients with favorable results from regional chemotherapy, 39% became resectable. This translates into a 12% resectability rate in the entire group of patients. Surgical procedures in long-term survivors are listed in Table 27.1. There were 15/80 (19%) Whipple resections, 12/80 (15%) corpus/tail

Table 27.1 Surgical procedures

	Patients	Percentage
Tumor resections	31/80	39
Whipple resection	15/80	19
Corpus/tail resection	12/80	15
Drainage of necrosis	4/80	5

Surgical procedures in long-term survivors of more than 1 year ($n = 80$)

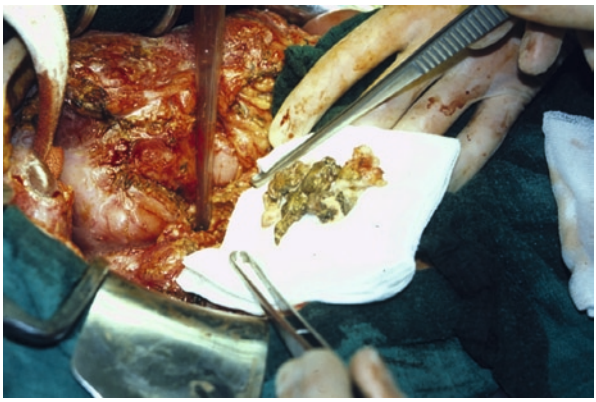

Fig. 27.2 Excavation and drainage of necrotic tumor tissue from the head of the pancreas after regional chemotherapy with DSM microembolization

resections, and 4/80 (5%) enucleations of necrotic tissues (Fig. 27.2). While resections were performed after downsizing of the primary tumor, enucleations had to be considered excavation of complete necrosis of the tumorous lesions, the symptoms of which were undulating fever, lethargy, lowering and unstable blood pressure, and high pulse rate, such as in tumor lysis syndrome. In the overall group of 265 advanced stage and partially pretreated patients, a 9 months median survival was noted. One year and 18 months survival was 30% and 25%, respectively. The paradox responsiveness of liver metastases versus primary tumors is also reflected in the causes of death. More or less every second patient (48%) died from tumor progression at the primary site and only 8% died from liver metastases, 7% from peritoneal dissemination, and 4% from lung metastases.

27.5 Discussion

During the last two decades achievements in terms of overall survival in the treatment of pancreatic cancer were not done in leaps, but were worked out in little steps only. The greatest little step forward was the introduction of gemcitabine in systemic chemotherapy for advanced and metastasized pancreatic cancer [1]. This was a landmark study, the results of which – an improvement of median overall survival from some 4–6 months – could be confirmed by a series of subsequent studies from other previously mentioned groups, and were not surpassed so far in overall survival by any other combination therapy. This includes conventional chemotherapeutic drugs as well as newer targeted agents. Studies conducted so far were based on the evaluation of the effect of various drug combinations on survival, in the form of trial-and-error testing, without considering potential advantages of modified handling of drugs such as manipulation of parameters like exposure and drug concentration at the target site.

Dose-dependent tumor toxicity of chemotherapeutics has been a well-known principle [36–39]. The dose–response behavior is steep [40]. In clinical practice with systemic chemotherapy, however, required drug exposures in solid tumors are limited by escalating toxicity. Therefore, the concentration component of the time x concentration product

maybe managed using techniques such as regional chemotherapy, the rationale behind which is to provide a means for delivering a much higher dose and concentration of the drug directly to the tumor than can be achieved by systemic administration.

When CT Klopp in 1950 first injected nitrogen mustard into an artery, the local effect appeared to him like "chemotherapeutic irradiation" [41]. This was the very beginning. During the years and decades since then, pitfalls with regional chemotherapy, in general, were associated with lack of experience in terms of know-how, techniques, and pharmaceutical and pharmacokinetic principles.

Therapy of pancreatic cancer in particular seemed to be an unsurmountable challenge. In recent years, progress has been made with regard to the local effect of intra-arterial chemotherapy on liver metastases [30–33]. This is most evidently due to the better blood supply as compared with the primary tumors in the pancreas that are encased in fibrotic tissue. This phenomenon was demonstrated impressively in second look operations 12 months after regional chemotherapy. Liver metastases, parapancreatic lymph node metastases, and the primary tumor itself showed a different histologic response behavior. Whereas in liver metastases, histologically, no more vital tumor tissue was observed, lymph node metastases showed central necrosis with some intact tumor cells in the periphery, the biopsy from the primary tumor, however, showed massive cytoplasmatic edema and marked tumor-cell degeneration, but altogether the least response [30]. This paradox response between primary tumor and metastases reveals the crucial weak point in the therapy of pancreatic cancer. Since a complete response in the primary can hardly be achieved, and most resections are R1 resections, the most frequent cause of death is relapse and tumor progression at the primary site [31]. Systemic chemotherapy, in what combination so ever, cannot provide the necessary drug exposure that is required. This maybe the reason why all combination therapies eventually failed.

Regional chemotherapy, however, provides an advantage in response rates in single studies with consistently elevated median overall survival times of 8–10 months with lower side effects, which should not be imposed on patients with poor life expectancy who suffer already enough from their disease. The prospective randomized phase III study from the Italian SITILO group clearly revealed the superiority of regional chemotherapy [25].

There is still a lot of potential of possible and necessary improvement, especially in the management of the resistant primary tumors. The problem is not solved by far yet. However, ongoing studies with microembolization and isolation techniques show a tendency toward improvement of the response behavior at the primary site (to be published).

Effective therapy of the primary tumor is particularly important in induction chemotherapy for borderline or non-resectable tumors [35]. Actually, there are no phase III trials available that clarify the effect of systemic or intra-arterial induction chemotherapy on resectability. Who judges and decides resectability? Decisions maybe individually different. Well-designed and reproducible parameters defining "resectability" are mandatory to decide which tumors are resectable and which are not. It largely depends on the experience and technical skills of the surgeon. Therefore, such a study can hardly be performed as a multicenter study unless the local therapeutic approach is so efficient that it really generates measurable downsizing or tumor necrosis, and therefore resectability.

Systemic chemotherapy is most unlikely to do so at present. Regional chemotherapy holds this potential, but still requires much improvement in order to overcome chemoresistance at the primary tumor site. Therefore, actually, progress is made in little steps and not yet by leaps.

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