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Chemotherapy in pancreatic adenocarcinoma

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Abstract. – Pancreatic cancer is a malignancy with a very poor prognosis, even when radically resected. In advanced disease chemotherapy has a role in terms of clinical benefit and symptoms palliation, more than survival advantage. Gemcitabine as a single agent is the first-line standard treatment since 1997. Several trials failed to demonstrate a survival advantage of chemotherapy doublets or gemcitabine combined with biological agents versus gemcitabine alone in phase III trials. Erlotinib was the only agent to produce a statistically significant improvement of survival when combined with gemcitabine versus gemcitabine alone. Nevertheless, the clinical application of these literature data remains controversial. However, a meta-analysis showed that combination chemotherapy is superior to gemcitabine alone in terms of survival and clinical benefit in selected subgroups of patients. In unresectable locally advanced disease chemotherapy is active, whereas no high level evidence exists about a possible superiority of chemoradiation. Chemotherapy followed by chemoradiation represents a promising treatment schedule, resulting better than chemotherapy alone in a retrospective analysis.

Adjuvant chemotherapy is nowadays a standard treatment, with both 5-FU and gemcitabine resulted superior to observation. Instead adjuvant chemoradiation is not a standard, even though it can be suggested in selected subgroups of patients. In resectable locally advanced disease neoadjuvant therapy is still investigational. Chemoradiation or chemotherapy followed by chemoradiation produced promising results in phase II trials. Possible future gain in terms of survival could come from better neoadjuvant treatments in potentially resectable pancreatic carcinoma. Therefore, this setting should stimulate studies with new drugs and combinations and potential biological predictive factors.

Key Words:

Pancreatic cancer, Chemotherapy of pancreatic neoplasms, Chemoradiation, Gemcitabine, 5-FU, Adjuvant, Neoadjuvant.

Introduction

Pancreatic carcinoma is a poor prognosis cancer and represents the fourth cause of cancer death worldwide. Surgery is the only potentially curative treatment, although the percentage of patients with resectable disease at diagnosis is just 10-20%. Even after a radical resection, the prognosis remains poor due to the high rate of local and distant recurrences, that exceed 80%. Therefore, the 5-year overall survival (OS) rate is lower than 20%[1-3].

The prognosis is obviously even poorer in patients with advanced disease, with a median OS of 4-6 months for metastatic and 8-10 months for unresectable locally advanced ones. Despite the advances in surgical and medical oncology research, the prognosis has substantially unchanged over the last decade.

Chemotherapy (CT) has a role both in advanced and resectable disease. Obviously its aim is different related to the specific setting: quality of life in the metastatic and longer survival in the perioperative one.

We are going to critically discuss the role of CT in the management of pancreatic carcinoma, and the possible future developments.

Advanced Pancreatic Adenocarcinoma

CT has demonstrated to gain a survival benefit over best supportive care in the treatment of advanced pancreatic adenocarcinoma. A recent meta-analysis by Sultana et al. analyzed 7 clinical trials comparing best supportive care and CT for a total of 432 patients: CT significantly reduced the risk of death by 36% with a Hazard Ratio (HR) of 0.64 (95% CI, 0.42 to 0.98; $p<0.05$)[4].

The vast majority of clinical trials, investigating CT, includes both unresectable locally advanced and metastatic pancreatic adenocarcino-

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ma. But the differences in terms of prognosis, clinical behavior and treatment options between the two subgroups should be considered.

Metastatic

The aim of CT in metastatic pancreatic carcinoma is the palliation of the cancer related symptoms (most frequently abdominal pain, asthenia, weight loss, anorexia), other than to prolong survival. Therefore, clinical benefit (CB) is one of the most important parameter considered in trial investigating treatment for advanced pancreatic carcinoma.

Gemcitabine (GEM) as single agent was approved by FDA in 1997 based on the results from Burris's trial[5], that demonstrated a significant benefit in favor of GEM compared with 5-fluorouracil (5-FU) in terms of OS, 1-year survival rate and above all CB.

In this study, the patients treated with GEM gained a 5.65 months OS, which resulted significantly longer than the 4.4 months of those who received 5-FU (p=0.0025) (Figure 1). Also 1-year survival rate was significantly higher in the patients receiving GEM (18% versus 2%). Finally, the response rate (RR) resulted not significantly better for GEM then 5-FU (5.9% versus 0%). Clinical benefit was the innovative concept related to the GEM FDA approval. In the Burris's study CB was calculated on the basis of modification of pain intensity, analgesic consumption, and Karnofsky performance status. GEM conferred a significantly major symptoms control than 5-FU (23.8% versus 4.8%, respectively).

The survival benefit added from GEM represents a debated aspect. For instance, the meta-analysis by Sultana et al did not report any significant difference in terms of OS between 5-FU and GEM[4].

During the last decade a lot of studies aimed to improve the results of GEM as single agent were performed. In particular, two research lines were: (a) GEM schedule modulation, and (b) combinations with other drugs (cytotoxic and/or biological agents). Standard GEM schedule is 30 min infusion[5]. Phase I and II studies demonstrated that a prolonged fixed dose rate (FDR) of GEM at a dose of 10 mg/m^2/min results in a higher intracellular accumulation of the active metabolite, gemcitabine triphosphate, improving the activity of the drug, but unfortunately even toxicity (mainly hematological)[6,7]. Fixed dose rate GEM was compared with standard GEM schedule both as a single agent[8,9] and in combination with Oxaliplatin[10,11].

A phase II study by Tempero et al, comparing FDR with 30 min infusion, showed a statistically significant advantage in terms of OS (8 vs 5 months; p=0.013), and 1 and 2-year survival rate in favor of FDR infusion[8]. However, the FDR is characterized by a higher rate of hematological toxicity which makes difficult to get a correct and regular drug administration. A more recent phase III study by Poplin et al.[11] compared standard GEM schedule with FDR GEM monotherapy and in combination with Oxaliplatin. The Authors observed a difference in favor of FDR, both in terms of survival (OS and PFS) and RR. Nev-

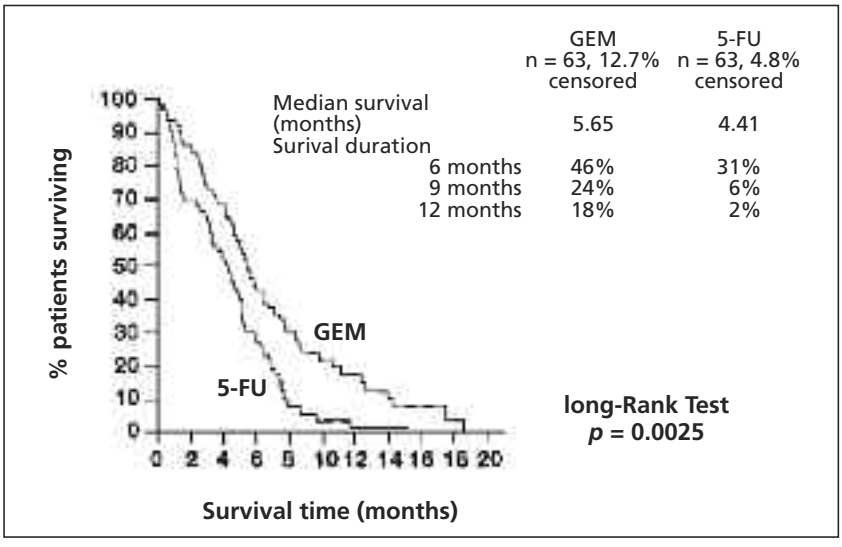

Figure 1. Survival difference between Gem and 5-FU in patients with advanced pancreatic carcinoma (Burris et al.[5]).

ertheless it was not statistically significant and furthermore FDR resulted more toxic, therefore not justifying the clinical use of FDR GEM instead of standard 30 min infusion.

A further not yet solved issue is the GEM combination treatment. A number of trials investigating the efficacy of GEM-based doublets have failed to demonstrate a survival advantage over GEM alone. Despite several phase II studies had showed promising results[12,13], any of the so far published phase III trials reported a significant improvement of survival when GEM was compared with chemotherapeutic combinations. Several cytotoxic agents were studied in combination with GEM versus GEM alone, such as Cisplatin and Oxaliplatin[10,14,15], Capecitabine[16,17], 5-FU[18], pemetrexed[19], irinotecan[20].

The study by Louvet et al.[10] showed a statistically significant advantage in terms of PFS, Overall Response Rate (ORR), and CB and a statistically non significant OS advantage in favor of GEM and Oxaliplatin (GEMOX) combination. The study by Herrmann et al.[16] comparing GEM and Capecitabine (GemCap) with GEM alone had similar results with an OS of 8.4 months in the combination arm versus 7.2 months in the GEM arm (p=0.234). Although an interesting finding was observed in a *post hoc* analysis, patients with a good performance status (ECOG = 0 and 1) obtained a statistically significant survival benefit from the addiction of Capecitabine (OS: 10.1vs 7.4 months; p=0.014). Only one study showed a survival advantage in favor of GemCap compared with GEM alone, with a median OS of 7.4 months versus 6 months (p=0.026), respectively; unfortunately it has never been published, after the presentation at ECCO 2005[17].

Despite the absence of clear improvements of the single agent GEM results, we should not consider combination CT completely *negative* due to the results of some recent meta-analyses[4,21,22]. Sultana et al reviewed the data from 19 studies for a total of 4697 patients. Overall survival was statistically better in favor of the combination arm with a 9% reduction of death risk and a HR of 0.91 (95% CI 0.85-0.97). The subgroup analysis confirmed that platinum compounds (HR 0.85; 95% CI, 0.74 to 0.96) and Capecitabine (HR: 0.83; 95% CI, 0.72 to 0.96) combinations performed better than GEM alone. Similar results emerged from two meta-analyses by Heinemann et al. The analysis, performed on 15 trials including a total of 4465 patients, confirmed that platinum- and fluropirymidine-based combinations achieved a significant survival advantage over GEM alone with a HR of 0.85 (95% CI: 0.76-0.96, p=0.010) and 0.90 (95 CI: 0.81-0-99; p=0.030), respectively. An additional analysis was performed in five trials with 1682 patients of whom data about performance status (PS) were available. It indicated that patients with a good PS had a marked survival benefit from combination CT (HR = 0.76; 95% CI: 0.67-0.87; p<0.0001), while the benefit was lost in the patients with initial poor PS (HR= 1.08; 95% CI: 0.90-1.29, p=0.40).

On the basis of the above mentioned data, single agent GEM remains the standard of first-line treatment of metastatic pancreatic carcinoma, even though in specific subsets of patients (e.g.: good PS, symptomatic) one should consider the use of combination treatment.

Biological agents, including anti-angiogenic, matrix metalloproteinases (MMP) inhibitors, and Epidermal Growth Factor Receptor (EGFR) inhibitors have also been extensively investigated in the treatment of pancreatic cancer, with poor results[23,24]. Both Bevacizumab[25,26] and Cetuximab[27] have failed to improve survival when combined with GEM versus GEM alone in phase III trials (REF). However, based on a phase III trial showing a survival advantage over GEM alone, Erlotinib (Tarceva) in combination with GEM was approved by FDA as first line treatment for advanced pancreatic carcinoma[28]. Nevertheless the survival gain observed in this study is very short (6.24 vs 5.91 months; p=0.038) (Figure 2), and therefore widely debated. For instance in Europe this combination was not registered by EMEA.

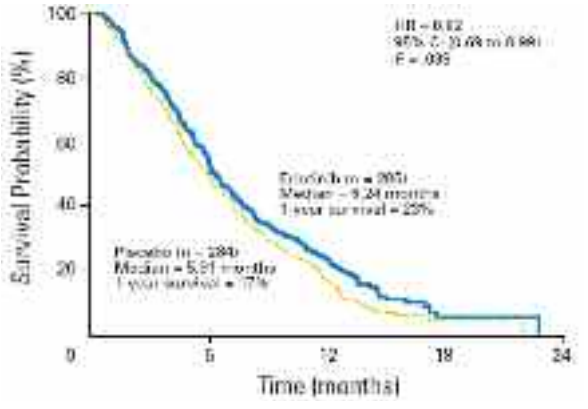

Figure 2. Overall survival in patients treated with GEM + Erlotinib versus GEM alone[28].

Locally Advanced

The optimal therapy for locally advanced pancreatic carcinoma is still controversial.

Radiotherapy (RT) (alone or in combination with CT) seems to improve both local tumor control and survival. Irradiation on pancreatic bed is limited by technical and anatomical issues causing high risk of gastrointestinal toxicity. Chemoradiation (CRT) has reported to be superior both to best supportive care and RT alone in terms of OS, PFS, and RR. By contrast, literature data of CRT versus CT are not conclusive[29-31]

A French study by Chauffert et al. comparing Cisplatin- and 5-FU-containing CRT followed by GEM with GEM alone failed to demonstrate a survival advantage in favor of CRT. The study accrual was prematurely interrupted due to the evidence of a shorter survival in the combined treatment arm, associated with a higher rate of grade 3 and 4 toxicity[32].

At the light of these conflicting data, a standard of treatment cannot be identified for locally advanced pancreatic cancer. A retrospective analysis by Huguet et al. suggested a possible treatment algorithm. The Authors retrospectively compared the survival of patient treated in phase II and III studies comparing upfront CT followed by CRT with CT alone. About 30% of the patients had a systemic progression of the tumor within the first three months after starting treatment. Among the remaining patients, those who received the combined treatment achieved a significantly better OS (15.0 vs 11.7 months; p=0 .0009) and PFS (10.8 vs 7.4 months; p=0.005), suggesting a role of sequential CT/CRT in improving the outcome of selected patients. The sequential schedule allows to select patients with a real locally advanced disease who are likely to benefit from a combined treatment, and avoids a useless CRT in those who have a systemic disease (about 30%)[33,34].

Locally Advanced Resectable Disease

Median OS after surgical excision is about 20 months and the 5 year survival rate does not exceed 20%. Chemotherapy was studied both as postoperative (adjuvant) and preoperative (neoadjuvant). Radiotherapy was also investigated in combination with CT in both settings.

Adjuvant

Postoperative CT is widely accepted as a standard of care in resected pancreatic carcinoma[35,36]. The ESPAC-1 trial demonstrated an advantage in favour of chemotherapy with 5-FU[37]. In that study, four arms were compared: CT, CRT, RT, and surgery alone. The primary aim of the study was to compare two different groups of treatment: CRT versus no CRT and CT versus no CT. Even with the limits related to the statistical design (2 × 2 factorial design) and the absence of a direct comparison between CT and surgery alone, the trial's results demonstrated a clear advantage in favour of adjuvant CT over no CT arm (OS: 20.1 vs 15.5 months, respectively; HR 0.71; 95% CI 0.55-0.92, p=0.009). The CONKO-1 trial (38), comparing GEM with observation, produced a statistically significant better PFS for GEM over surgery alone (13.4 vs 6.9 months, respectively; p<0.001), and not statistically significant better OS (22.5 vs 20.5 months, respectively). The ESPAC 3 trial[37] compared adjuvant 5-FU with GEM. No survival statistically significant difference was observed between the two arms, with 23 versus 23.6 months OS in 5FU/Folates and GEM arms, respectively[39].

Adjuvant CRT is, even in this setting, controversial. In the North America, 5FU-based CRT is considered the standard of treatment, on the basis of the results of a Gastro Intestinal Tumor Study Group (GITSG) trial. In this trial, adjuvant 5-FU-based CRT followed by 5-FU over 2 years resulted in a longer survival than surgery alone (20 versus 11 months, respectively); this advantage was confirmed by a further study by Yeo et al.[40,41].

The results of these trials were not confirmed by further studies[37,42]. In the EORTC trial a not statistically significant trend for a survival advantage in favour of CRT over surgery alone was observed. In the ESPAC-1 trial, the CRT appeared to be detrimental with a statistically significant lower survival in comparison to no CRT arm (15.9 vs 17.9 months, respectively; p=0.05).

Nevertheless, retrospective analyses[43] and meta-analyses[44,45] showed that CRT can offer a survival and disease control benefit in patients with non-radical resection (R1 surgery).

In conclusion adjuvant CT is the standard of care for patients with a radically resected pancreatic carcinoma. Chemoradiation can be considered in selected patients with R1 surgery.

Neoadjuvant

Neoadjuvant therapy, in resectable locally advanced pancreatic carcinoma, is still under investigation. A number of phase II trials' results sup-

port its activity and feasibility (even in combination with RT)[46-49], but phase III trials comparing neoadjuvant therapy to surgery alone are still lacking[50]. A comparative study by Spitz et al. reported similar outcome for patients receiving neoadjuvant and adjuvant CT[51].

The primary aims of preoperative CT are to downsize the tumor, and to improve the rate of R0 surgery. On the other hand, preoperative treatment allows to "select" patients who could really benefit from surgery, excluding those with an early systemic spread of disease. Furthermore, the early timing of chemotherapy allows to treat all the eligible patients, avoiding dropouts or delays due to surgery-related complications; in fact about 25% of resected patients do not receive adjuvant CT for these reasons.

As above mentioned, several trials have investigated the role of neoadjuvant CT and CRT. CT has demonstrated promising activity, as combination treatment (e.g.: GEM-Cisplatin doublet)[46,47]. Also combined treatment (CT plus RT) appears to be worth of further investigation. Trials evaluating GEM-based CRT demonstrated high rate resectability and prolonged survival, with acceptable toxicity. Chemotherapy followed by CRT was evaluated in phase II trials with promising results[52].

Finally, over the last years EGFR inhibitors (Erlotinib and Cetuximab) have been demonstrating to enhance the activity of GEM-based CRT, representing a novel and promising combination treatment even in the neoadjuvant setting. A recent Phase II study, presented at ASCO 2008 demonstrated that GEM and Cetuximab combination with concomitant RT produced acceptable toxicity with high rate RR and R0 resection[53-55].

Conclusion

Chemotherapy has an important role in pancreatic adenocarcinoma. Gemcitabine as a single agent represents the standard first-line treatment of metastatic pancreatic carcinoma since 1997, due to a favourable comparison with bolus 5FU. Nevertheless, this advantage was not confirmed by a meta-analysis, that did not report any statistically significant difference in terms of OS in favour of GEM versus 5-FU. Furthermore, given that bolus 5FU has been reported inferior to continuous infusion schedules of 5FU in colon carcinoma, capecitabine or protracted continuous infusion 5FU could be supposed equally or better active than GEM. However, the GEM FDA approval in pancreatic cancer represented the first decision based also on clinical benefit, and therefore it represented a promising beginning in oncological drugs regulatory field.

Gemcitabine-based combinations, both with chemotherapeutic and biological agents, cannot be considered as a standard of care considering the results of the phase III trials, even though erlotinib showed a minimum statistically significant advantage. Nevertheless, the use of combination chemotherapy could be considered in selected subsets of patients, based on the results of somemeta-analyses. In particular, GEM-based doublets containing platinum compounds or capecitabine could be justified in selected patients with a good PS and with cancer related symptoms, in order to obtain a longer survival and better quality of life.

The treatment of locally advanced pancreatic carcinoma is a debated issue: CRT (both GEM- and 5FU-based) has been reported effective, more than RT, but not definitely superior to CT alone. Some prospective trials demonstrated an advantage in favour of CRT, whereas others showed a detrimental effect of CRT. The sequential treatment with CT followed by CRT, as retrospectively studied by the GERCOR group, resulted a promising treatment option for locally advanced pancreatic cancer. The results of this study, with the statistical limits of a retrospective analysis, suggested that CRT can improve survival over chemotherapy alone in patients with locally advanced disease. The induction CT allows avoid useless CRT in those patients with an early systemic progression, who represent about 30% of the patients with an initial diagnosis of locally advanced pancreatic cancer.

In the perioperative setting there are strong evidences supporting the efficacy of adjuvant CT, while neoadjuvant treatment should still be considered as investigational.

Adjuvant CT is the standard of care in Europe. Both 5-FU and GEM demonstrated to be effective in separate trials; no differences between the two drugs was observed in a recent comparative trial (ESPAC-3). Adjuvant CRT is the standard of care in North America, on the basis of a GITSG trial. However, it is not clear whether the advantage was due to the addition of RT or protracted CT administration. On the other hand, CRT can be justify in patients with a R1 resection.

Considering that the gain of survival obtained with adjuvant CT was minimum the neoadjuvant setting became a very interesting filed of research. At the present time neoadjuvant therapy is still investigational in potentially resectable locally advanced pancreatic carcinoma. As in locally advanced unresectable also in resectable pancreatic cancer CRT is probably better than CT in terms of RR and reduction of recurrence risk. Recent data about EGFR inhibitors in combination with GEM-based CRT are very promising and worthy of further investigation in this setting, where the RR is the main aim of treatment. Furthermore, sequential treatment (CT followed by CRT) should be considered even in the preoperative setting, considering that this approach allows to avoid useless, and potentially toxic, CRT and, worse, surgery, for patients with early systemic progression of disease.

In conclusion, the prognosis of pancreatic cancer remains poor both due to advanced stage at diagnosis and to high rate of recurrences. Well-designed studies, including biological investigations of possible predictive factors of response to chemotherapy and/or molecular targeted therapies represent a urge need.

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