

CONFERENCE REPORT

New Therapies for Pancreatic Cancer: Current Standard

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At the time of the diagnosis of pancreatic adenocarcinoma, about 10% of patients present with disease confined to the pancreas and are eligible for surgical resection while 90% of patients present with locally advanced (30-40%) or metastatic (50-60%) disease.

Resectable Disease

With regard to resectable disease, two recent phase III randomized trials showed that postoperative chemotherapy, either 5-fluorouracil or gemcitabine, significantly prolongs overall and disease-free survival with respect to observation alone [1, 2]. A Radiation Therapy Oncology Group (RTOG) phase III randomized trial showed significantly better survival after gemcitabine chemotherapy with respect to continuous infusion 5-fluorouracil in the subgroup of patients with pancreatic head cancer [3]. However, in this trial the dose of 5-fluorouracil was suboptimal, representing about 60% of the potential dose previously used in advanced disease [4] and a definitive conclusion about the superiority of gemcitabine can not be drawn. The findings from these trials confirmed that failure to prevent metastases represents the main pattern of disease recurrence even in the early stages of pancreatic carcinoma. While local recurrence is also the rule, isolated local failure occurred in less than one-third of cases. Accordingly, systemic chemotherapy appears to have a stronger rationale as a first postoperative therapy with respect to local treatment and either gemcitabine alone or full

dose 5-fluorouracil may be considered a standard. An ongoing European Study Group of Pancreatic Cancer (ESPAC-3) trial comparing gemcitabine to 5-fluorouracil-leucovorin postoperative chemotherapy should provide further information for resolving this controversy. The use of postoperative combination chemotherapy outside of clinical trials is unjustified. No firm conclusion about the role of modern chemoradiation after systemic chemotherapy is possible because no information from phase III trials is available. In fact, randomized trials comparing chemoradiation with observation used outdated modalities, for both radiation and chemotherapy, and administered this local treatment as an upfront postoperative treatment [2, 5, 6]. Despite these methodological pitfalls, controversial results were observed. Thus, it is the author's opinion that modern chemoradiation after systemic chemotherapy has a role in the therapeutic management of this disease. An ongoing European Organisation for Research and Treatment of Cancer (EORTC) trial, comparing four cycles of gemcitabine with two cycles of gemcitabine followed by chemoradiation will contribute to better clarifying this issue.

Locally Advanced Disease

Systemic therapy has been accepted as a standard in early stage pancreatic cancer. A logical consequence is that locally advanced disease should be treated with systemic chemotherapy as well. In effect, virtually all

patients with stage III pancreatic cancer will ultimately develop metastatic disease. Considerations about upfront chemotherapy are similar to metastatic disease and are reported below. Chemoradiation seems to have a role as a consolidation treatment for patients who do not have progressive disease during chemotherapy. This approach significantly improved survival from 12 to 15 months in a retrospective analysis of data from phase II-III trials on stage III disease in the Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic (GERCOR) experience [7].

Metastatic Disease

Until a decade ago, a nihilistic attitude prevailed, raising the dilemma as to whether patients with advanced pancreatic cancer should receive any systemic treatment at all [8, 9]. Afterwards, two trials comparing chemotherapy with best supportive care suggested that chemotherapy may improve survival time and the quality of life [10, 11]. Further progress was obtained by using of gemcitabine [12]. Despite the lack of confirmatory trials and the numerous methodological pitfalls of the pivot trial such as the absence of a prospective statistical design, the use of a not validated primary endpoint (clinical benefit), limited statistical power for the secondary endpoint survival due to the small number of patients (n=126), the use of a debatable comparative arm and of a subjective definition of progressive disease (clinical status which was consistent with disease progression) which may constitute a bias in a single blind study, gemcitabine became a standard of care in advanced pancreatic cancer. Gemcitabine achieves an objective response rate of 4-26%, a median progression-free survival of 2.0-3.8 months and a 1-year overall survival of 17-28% [13, 14, 15, 16, 17, 18, 19, 20]. The therapeutic activity of gemcitabine administered as a fixed-dose rate infusion instead of the standard 30-minute infusion did not significantly improved the outcome of patients with advanced pancreatic cancer [13].

The addition of a second cytotoxic agent or other drugs to gemcitabine did not improve treatment efficacy over single agent gemcitabine [13, 14, 15, 16, 17, 18, 19, 20, 21]. A meta-analysis revealed that the addition of 5-fluorouracil, cisplatin or a platinum compound to gemcitabine may improve 1-year overall survival by 4% [22].

After a decade of unfruitful attempts, two gemcitabine-based doublets yielded a statistically significant outcome improvement over a single agent in phase III trials [23, 24]. However, the results of the capecitabine-gemcitabine combination were not confirmed in another phase III trial [25]. Altogether, the advantage obtained by capecitabine-gemcitabine and by a gemcitabine-erlotinib combination in overall survival was of marginal clinical significance, consisting of an absolute 7% improvement at one year (from 17-19% with gemcitabine alone to 24-26% with combined therapy) [23, 24]. Overall, from a clinical perspective, these trials confirmed the lack of a significant impact of double-agent combination therapy on the clinical course of pancreatic cancer.

On the other hand, a cisplatin, epirubicin, 5-fluorouracil, and gemcitabine (PEFG) regimen was proved to be both clinically and statistically more effective than single agent gemcitabine as an upfront treatment in advanced pancreatic cancer [26]. The superiority of the four drug regimen over the single agent gemcitabine was shown in terms of response rate (38.5% vs. 8.5%), median progression-free survival (5.4 vs. 3.3 months), clinical benefit (65% vs. 25%) and 1-year overall survival (38.5% vs. 21.3%). Interestingly, the survival improvement was not achieved at the cost of impaired quality of life [27]. The toxicity of the PEFG regimen mainly consisted of short-term and uncomplicated neutropenia and thrombocytopenia [28]. The findings of the phase III trial confirmed previous phase II results [28] and were reproduced in two subsequent series [29, 30] treated by a simplified schedule which had a better toxicity profile and was more suitable for clinical use. An ongoing trial is evaluating the substitution of

infusional 5-fluorouracil with oral capecitabine in an attempt to further improve the effect of the regimen.

Although by enlarging the sample size, any difference may become statistically significant, the driving force for selecting a standard treatment should remain the clinical relevance of improvement. Accordingly, and despite the scarce appeal of 'old' drugs, a large confirmatory trial exploring the PEFG regimen as the best candidate cornerstone for the addition of targeted therapies appears worthwhile.

Keywords capecitabine; Drug Therapy; erlotinib; Fluorouracil; gemcitabine; Pancreatic Neoplasms; Radiotherapy; Review; Therapeutics

Abbreviations EORTC: European Organisation for Research and Treatment of Cancer; ESPAC: European Study Group of Pancreatic Cancer; GERCOR: Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic; PEFG: cisplatin, epirubicin, 5-fluorouracil, gemcitabine; RTOG: Radiation Therapy Oncology Group

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