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REVIEW ARTICLE

Management of unresectable, locally advanced pancreatic adenocarcinoma

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Abstract The diagnosis of unresectable locally advanced pancreatic adenocarcinoma (LAPC) requires confirmation, through imaging tests, of the unfeasibility of achieving a complete surgical resection, in the absence of metastatic spread. The increase in overall survival (OS), together with an appropriate symptom management is the therapeutic target in LAPC, maintaining an acceptable quality of life and, if possible, increasing the time until the appearance of metastasis. Chemoradiation (CRT) improves OS compared to best support treatment or radiotherapy (RT) but with greater toxicity. No significant increase in OS has been achieved with CRT when compared to chemotherapy (QT) alone in patients without disease progression after four months of treatment with QT. However, a significantly better local control, that is, a significant increase in the time to disease progression was associated with this approach. The greater effectiveness of the schemes FOLFIRINOX and gemcitabine (Gem) + Nab-paclitaxel compared to gemcitabine alone, has been extrapolated from metastatic disease to LAPC, representing a possible alternative for patients with good performance status (ECOG 0–1). In the absence of randomized clinical trials, Gem is the standard treatment in LAPC. If disease control is achieved after 4–6 cycles of QT, the use of CRT for consolidation can be considered an option vs QT treatment maintenance. Capecitabine has a better toxicity profile and effectiveness compared to gemcitabine as a radiosensitizer. After local progression, and without evidence of metastases, treatment with RT or CRT, in selected patients, can support to maintain the regional disease control.

Keywords Unresectable · Locally advanced · Pancreatic ductal adenocarcinoma · Chemotherapy · Radiotherapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, is currently the third leading cause of cancer, and it has been estimated that it may rank second from 2020 [1, 2]. In 2008, PDAC was diagnosed to 70,000 patients in Europe, with a five-year survival of 7.2% [3]. Complete tumor extirpation (R0 resection) remains the best possibility for long-term survival in patients with PDAC. Unfortunately, approximately 80% of patients are not amenable to resection at diagnosis either because of metastatic (40%) or locally advanced disease (40%) [4].

This article is the result of the GALLgo project, an advisory project conducted by the ECO Foundation from September to December 2015 intended to address improvements in the therapeutic approach for patients with

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pancreatic cancer. More than forty medical specialists involved in the multidisciplinary approach to patients with pancreatic cancer, including medical oncologists, radiation therapists, surgeons, radiologists, pathologists, endocrinologists, and palliative care specialists, participated in the GALLgo project. These recommendations are based on the results of clinical trials, retrospective, observational studies, as well as the group of experts' opinion (levels of evidence: quality of evidence: I–III; strength of recommendation: A–E) [5].

The purpose of this article is to review the objectives of treatment of unresectable, locally advanced pancreatic adenocarcinoma (LAPC) and the therapeutic options available [chemotherapy (QT), radiotherapy (RT) or chemoradiotherapy (CRT)].

Definition and diagnosis

Those PDAC that invade adjacent structures, usually vascular invasion, and in which complete tumor removal is not feasible, without evidence of metastatic disease in imaging studies for staging at diagnosis are classified as unresectable LAPC [6]. There are different classifications based on consensus that define the unresectability criteria such as the guideline of the National Comprehensive Cancer Network [7].

Unresectability criteria must be evaluated in Multidisciplinary Tumor Committees to guide patient's treatment, in a consensual way (IIIA). For a correct evaluation of the vasculature a multiphase computed tomography scan (CT) of the thorax, abdomen and pelvis performed in arterial and venous phase is recommended. The use of other imaging tests should be evaluated in individual basis (IIA). Histopathological diagnosis is essential before any therapeutic intervention is performed (IIIA).

Treatment of LAPC

The aim of LAPC treatment is to improve overall survival and quality of life through symptom control, for which better local disease control is required. Treatment of these patients is controversial because most of the studies conduct a combined analysis of patients with LAPC (between 20 and 30%) and metastatic disease, and no specific subanalysis for this subgroup of patients are currently available. Enrolment into clinical trials is the priority strategy to find the answers to pending questions. The clinical guidelines recommend chemotherapy as the initial approach in patients who are candidates to receive, to select patients who experience rapid dissemination [7, 8] (IIB).

Chemotherapy

In patients diagnosed with LAPC, a comprehensive initial work-up should be performed including: nutritional status; baseline performance status; symptom burden; active comorbidity and potential adjustment of their treatment; biliary tract patency and need for diversion or stent; geriatric assessment in patients >70 years of age (IIIA). Once patients are assessed and management of their baseline state and disease has been adequately optimized, they will be classified as:

1. *Patients suitable for chemotherapy treatment without limitations* The presence of all the following factors is required: ECOG 0–1; Age ≤75 years; normal liver function; good nutritional status.
2. *Patients suitable for chemotherapy with limitations* The presence of at least one of the following factors is required: ECOG 2; Age ≥75 years; impaired liver function; limited comorbidity that does not contraindicate chemotherapy; severe malnutrition.
3. *Patients not suitable for chemotherapy* The presence of at least one of the following factors is required: ECOG ≥3 (and possibility of reversal to ECOG ≤2 is ruled out); severe comorbidity that contraindicates chemotherapy (IIIB).

There are no randomized clinical trials aimed to assess the best therapeutic option in LAPC. The recommendations are based on extrapolations from randomized trials in patients with metastatic disease [9, 10], subgroups analysis of studies that included both LAPC and metastatic patients [11] or cases series, usually from one single institution and with a very limited number of patients analyzed [12] (IIIB). There is no current scientific evidence to support the use of a particular QT schema. Patient's preferences and priorities need to be taken into account individually (Fig. 1).

Patients suitable for chemotherapy treatment without limitations

Polichemotherapy treatment is recommended. The recommended regimens are FOLFIRINOX [9, 12] and the combination of Gemcitabine (Gem) plus Nab-paclitaxel [10]. Both schemas have demonstrated a significant increase in survival and response rate in phase III randomized studies, compared to Gem alone in patients with metastatic disease (IIIB). The PRODIGE4/ACCORD11 clinical trial demonstrated an increase in overall survival (OS) (HR: 0.57) with FOLFIRINOX schema vs. Gem alone as first line treatment in patients with metastatic disease, with good performance status (ECOG 0–1) and age <76 years [9]. The IMPACT study, with naive metastatic patients, without age limit and a Karnofsky performance status ≥70% were randomized to

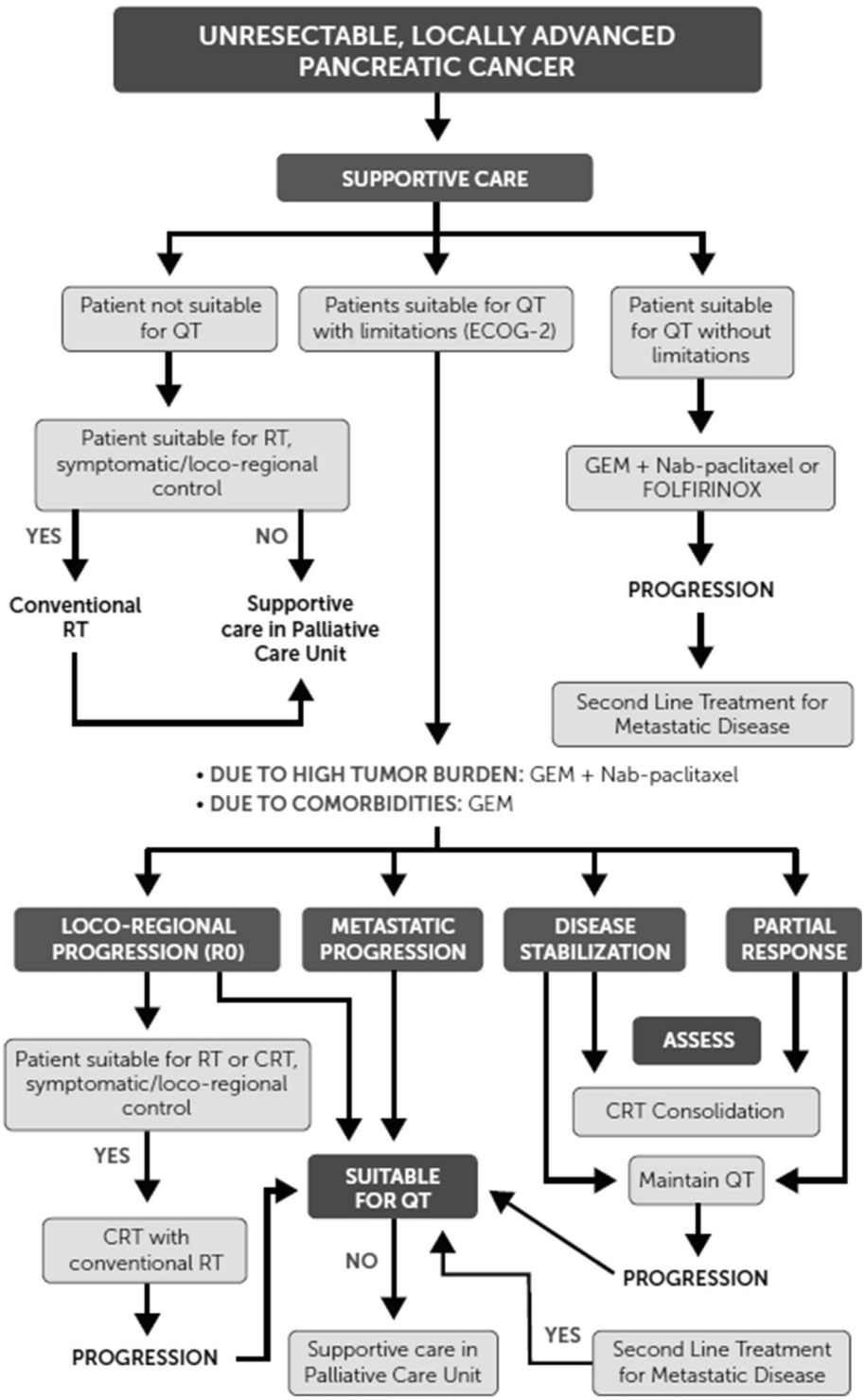

Fig. 1 Treatment of LAPC

first line treatment with Gem or Gem + Nab-paclitaxel [10]. The primary aim, OS, was significantly better in the combination arm (HR: 0.72). Tumor response was significantly higher in both primary tumor and metastasis [13]. The toxicity associated to both schemas, although with a different profile, was superior compared to Gem alone [9, 10].

Patients suitable for chemotherapy with limitations

Administration of Gem [14], as monotherapy (IB) or combined with Nab-paclitaxel [10] (IIIB), is recommended. Combined treatment with Gem and erlotinib has shown no relevant clinical benefit in the subgroup of LAPC patients compared to Gem alone (HR: 0.94) in phase III

study that included both LAPC and metastatic disease patients [11]. If there is absolute contraindication for the use of Gem, treatment with fluoropyrimidines (capecitabine or 5-FU) is recommended (IIB).

Although treatment duration has not been established it will depend on tolerability and response achieved. Response assessment using CT scans every three months of treatment is recommended. It is recommended to continue treatment until disease progression, in the absence of toxicity and with a good tolerability.

Chemotherapy concomitant with radiotherapy

Local disease control is one of the primary aims in LAPC because patients are more susceptible to develop complications related to local disease growth, regardless of the development of distant metastasis. Initial treatment with RT was based on this idea of local growth control. The use of QT treatment as radiosensitizer, increasing toxicity of radiotherapy over tumoral cells made chemoradiotherapy (CRT) one of the valid options in LAPC. The biological basis of these effect is attributed to their ability to decrease the number of tumor cells in phase S, during which the cells are resistant to radiotherapy [15]. The combination of 5-FU and radiotherapy vs. radiotherapy alone was compared in the randomized studies, with contradictory results regarding the superiority of CRT in OS [16, 17]. The use of GEM or capecitabine concomitant to radiotherapy have shown, in randomized studies conducted in a limited number of patients, to achieve similar results compared to those of 5-FU, with different toxicity profile [18, 19]. To date, the phase III studies comparing CRT vs. RT have provided conflicting results [20, 21].

Two meta-analysis have compared CRT vs QT alone and have not shown any benefit with regards to OS with the combination treatment; however, an increase in toxicity was reported. Both meta-analyses include studies with great heterogeneity, which makes questionable the results achieved [22, 23].

The use of CRT is not recommended as initial treatment in LAPC (IIC). Its use should be reserved for selected patients with local progression, without evidence of metastatic disease, after having received QT treatment. Prior evaluation in the multidisciplinary committee is advised (IIIB).

Integration of concomitant CRT

Approximately 30–50% of LAPC patients develop metastasis in the first three months of follow-up. Treatment with QT allows the selection of patients who will be able to obtain the greatest benefit from CRT, because patients who develop metastases during prior chemotherapy, i.e., those with more aggressive tumors, will be excluded. It also allows for early control of eventual systemic disease, and delays aggression of CRT in initially more fragile patients. A systematic review concluded that, in selected patients, chemotherapy prior to CRT increases overall survival [22, 24, 25].

The results of the retrospective study conducted by Huget et al. [24] showed a median survival of 15 months with induction QT followed by CRT, for those who responded or experienced disease stabilization, vs. 11.7 months in the QT treatment arm ($p = 0.0009$). Prospectively Mukherjee et al. conducted a randomized study phase II study that compared CRT with Gem vs. CRT with capecitabine as consolidation treatment after three cycles of induction QT with Gem and capecitabine, respectively [19]. As a result, the arm of CRT and capecitabine as sensitising, obtained a survival upper middle (13.4 months vs. 15.2).

The LAP0726 study analyzed the role of RT and erlotinib in the LAPC setting [26]. A total of 442 patients were randomized to QT induction with Gemcitabine vs. Gemcitabine–erlotinib and subsequently, in the absence of progression, each arm was randomized to follow the same scheme of QT vs. CRT with capecitabine. No statistically significant differences in OS were observed, and therefore, the results were considered to be negative. CRT was associated with a decrease in the rate of local progression (32 vs. 46%, $p = 0.03$), a significant improvement in median delay to treatment reintroduction in CRT arm (6.1 vs. 3.7 months, $p = 0.017$) and a tendency to a longer progression-free survival (9.9 vs. 8.4, $p = 0.055$) [26].

The results of the reported studies and meta-analyses do not support this approach, but these are heterogeneous studies where the chemotherapy regimens currently known to be most effective were not used [22, 27, 28].

According to standard clinical practice, assessment of treatment response at three months is recommended. If disease control at three–six months (stable disease or partial response) is achieved with chemotherapy, each case should be individually assessed at the Multidisciplinary Tumor Committee without ruling out local treatment. In these cases, chemotherapy maybe continued until tumor progression or toxicity occur, but consideration of CRT is acceptable (IIA).

Radiotherapy

The significance of radiotherapy in the treatment of LAPC lies in the potential local control of the primary tumor, as well as symptom relief in treatments with palliative intent (Fig. 1). Today, due to recent scientific and technical advances, IMRT and SBRT have been established as highly effective and safe treatment procedures in multiple

sites, including pancreas. In this regard, there are phase II and retrospective studies where SBRT has shown its potential in the treatment of LAPC [29, 30]. SBRT is an emergent technique, and the evidence available so far shows its efficacy and safety in the treatment of LAPC. The short duration of the treatment is an advantage for the patient and also very convenient for the radiotherapy department. It is currently recommended in the context of clinical trials (IIIA).

Indications of radiotherapy in LAPC include:

(a) Treatment of patients who are not candidates for chemotherapy in whom local and/or regional control of disease is intended to be achieved or who require symptom palliation.
(b) Patients who, after induction chemotherapy, have sustained stable disease or partial response and QT is contraindicated (i.e., due to toxicity).
(c) The potential benefit of radiotherapy must be individually assessed in patients with non-metastatic progression after induction chemotherapy and subsequent QT contraindication (i.e., due to toxicity).

If there is no contraindication for QT always consider administration of CRT vs RT alone.

Conclusions

Assessment of unresectability in patients with LAPC should be established by a Multidisciplinary Tumor Committee, once all the required imaging tests as well as anatomo-pathological diagnosis have been performed (IIIA). The goal to pursue in the LAPC is the increase in OS, preserving the quality of life of the patients. For that, it is very important to achieve good local disease control. Initial treatment of LAPC is controversial due to the absence of phase III randomized studies to clarify this issue. Inclusion in a clinical trial is the best option whenever available. Initial treatment with QT is recommended (IA). There is no evidence which is the best scheme. By extrapolation from phase III studies in metastatic disease, FOLFIRINOX or the combination of Gem + Nab-paclitaxel may be considered for patients with ECOG 0–1 and with adequate comorbidity profile (IIIB), although LAPC standard treatment is QT with Gem (IB). After response or stabilization to QT induction (4–6 months) consolidation with CRT is an alternative to maintenance treatment with QT in selected patients (IIB). In patients who maintain good performance status with local progression, without metastases, locoregional treatment with CRT or RT alone, for those cases where QT is contraindicated, can be considered (IIIC).

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Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

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