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Review article

Management and supportive treatment of frail patients with metastatic pancreatic cancer

Macarulla T.[a,*], Carrato A.[b], Díaz R.[c], García A.[d], Laquente B.[e], Sastre J.[f], Álvarez R.[g], Muñoz A.[h], Hidalgo M.[i]

[a] Dpt. Medical Oncology, Hospital Vall d'Hebrón, Barcelona, Spain
[b] Dpt. Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain
[c] Dpt. Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain
[d] Dpt. Medical Oncology, Instituto Catalán de Oncología, de Girona, Spain
[e] Dpt. Medical Oncology, Instituto Catalán de Oncología, L'Hospitalet de Llobregat, Barcelona, Spain
[f] Dpt. Medical Oncology, Hospital Clínico Universitario San Carlos, Spain
[g] Dpt. Medical Oncology, Centro Integral Oncológico Clara Campal, Hospital Universitario Sanchinarro, Madrid, Spain
[h] Dpt. Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[i] Dpt. Medical Oncology, Beth Israel Deaconess Medical Center, Boston, USA

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ABSTRACT

Data regarding management of frail patients with pancreatic ductal adenocarcinoma practice is currently very scarce. Randomized clinical trials usually exclude these subgroup of patients and the majority of the publications only consider chronological age and ECOG performance status for their classification. Therefore, the current available data do not reflect daily clinical practice. Only data from a phase two study (FRAGANCE study), designed to select a tolerable dose-schedule of nab-placitaxel + gemcitabine (Phase one) and to evaluate the efficacy of the selected regimen (Phase two) in patients with ECOG-2 and previously untreated advanced PDAC, are currently available. Management of these particular patients is exceedingly complex and requires collaboration of multidisciplinary teams and intensive support treatment. This article reviews the literature available regarding the management of the so-called frail patients and provide guidance for chemotherapy as well as supportive care treatments.

Contents

* Corresponding author at: Pg Vall d'Hebrón 119, Barcelona, Spain.
E-mail address: tmacarulla@vhio.net (T. Macarulla).

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents approximately 3% of all cancer diagnosed worldwide yearly [1]. PDAC is a very aggressive disease that is usually diagnosed in advanced stages (stage four) and has a very poor five-year overall survival. >50% of these patients are managed with palliative systemic chemotherapy [1].

After several decades of stagnation in the systemic treatment of this disease, two recent randomized clinical trials have demonstrated statistically significant and clinically meaningful improvement in survival in patients with advanced PDAC. Indeed, both the ACCORD-11/PRODIGE phase three trial, using FOLFIRINOX (Combination of 5- Fluorouracil+ leucovorin + irinotecan + oxaliplatin), and the MPACT phase three trial, with a combination of gemcitabine (GEM) and nab-paclitaxel, showed an improvement in median survival as compared to GEM alone. However, these treatments were also associated with an increase in toxicity related events [2, 3].

The goal of chemotherapy treatment is to achieve an adequate balance between toxicity and efficacy. This is even more important in PDAC given the high morbidity caused by the disease and the limited benefit of chemotherapy treatment. For this reason, clinical trials are very restricted in the eligibility criteria and focus only in patients with higher likelihood of obtaining a clinical benefit. Thus, for example, the ACCORD-11/PRODIGE trial restricted enrollment to patients <75 years old and with Eastern Cooperative Oncology Group (ECOG) of zero-one. While MPACT was more permissive, with no age restriction and allowing Karnofsky Index (KPS) performance status of 70% [equivalent to Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2] [4], it still enrolled a very selected patient subgroup that does not reflect daily clinical practice.

In the near future, approximately 70% of all cancer diagnoses will occur in patients age 65 or older. Older patients receive chemotherapy less frequently and their participation in clinical trials is lower compared to other age groups despite the results of recent observational studies that encourage the participation of this age group in therapeutic trials [5, 6]. In addition, very limited data is available from clinical trials regarding this patient population. Management of these patients is exceedingly complex and requires the collaboration of multidisciplinary teams and aggressive supportive treatment that must include a geriatric assessment. This manuscript is the result of the GALLgo project, a consultant initiative carried out by the ECO Foundation.

In this article, we provide a summary of the literature as well as experts´ opinion regarding the management of the so-called frail patients and provide guidance for both chemotherapy as well as supportive care treatment.

1.1. Definition of Frail Patient With PDAC

The classic definition of a frail patient has been associated with older age (65, 70 or 75 years in different studies) or with deteriorated general health status (ECOG ≥2 or KPS ≤ 70%). Over the last few years, however, the concept of frailty is being used in a broader way and not limited to chronological age. According to the American Medical Association (AMA), the term "frailty" characterizes "the group of patients that presents the most complex and challenging problems to the physician and all health care professionals", because they have a higher susceptibility to adverse outcomes such as mortality and institutionalization [7]. Multiple factors, summarized in Fig. 1, contribute to the concept of frailty. In patients with metastatic PDAC it is critical, however, to differentiate the factors that are associated with the disease itself (intense pain, asthenia, cachexia) as the main cause of the frail condition and, therefore, amenable to improve with specific chemotherapy treatment, from those factors associated with pre or coexisting conditions that limit and sometimes contraindicate chemotherapy treatment (Table 1) [8–14]. As of today, the information regarding this group of patients is scarce and the majority of published trials keep using chronological age and ECOG performance status as eligibility criteria and in the statistical analysis.

PDAC median age for presentation is >70 years and patients affected for this tumor in a high frequency are 70 years old or older. This population presents with some past medical history than can affect the general status of the patient. In this sense, the collaboration between the medical oncologist and the geriatric assessment team is essential.

1.2. Analysis of Frail Patients With PDAC Included in Clinical Trials

As discussed above, patients with PDAC often present with deteriorated overall health status either secondary to the PDAC itself or because of associated comorbidities. These patients, who are frequently seen in daily practice, are not well represented in clinical trials. Their management, therefore, entails significant difficulties, as it is not clear how to infer what would be the activity and toxicity of regimens that have been developed in more fit patients.

1.2.1. Burris et al. Study

The study of Burris et al., published in 1997, evaluated in 127 patients with advanced PDAC whether GEM in monotherapy was superior to 5-fluorouracil (5-FU)/Leucovorin (LV) in terms of clinical benefit, objective response, and survival or progression of the disease [15]. The patients enrolled in the study presented a mean age of 60 years old and most of them had an impaired performance status at entry (a KPS of 50 to 70 was recorded in 70% and 68% patients randomized to GEM and 5-FU treatment, respectively. The primary aim of the study was clinical benefit (sustained improvement of ≥ four weeks in at least one of the parameters without worsening any other). The parameters used included: pain scale, performance status according to KPS, and weight [15]. Clinical benefit response was achieved in 23.8% of GEM-treated patients compared to 4.8% of 5-FU-treated patients ($P = .002$). The median survival (OS) was 5.65 and 4.41 months for GEM-treated and 5-FU-treated patients, respectively ($p = .002$). Response rate (RR) in GEM-treated patients was 5.4% compared to 0% in 5-FU treated patients. With regards to progression free survival (PFS), median PFS in the GEM-treated patients was 2.33 months vs. 0.92 months in the 5-FU treated patients ($p = .000$). This study demonstrated that GEM confers a better clinical benefit compared to 5-FU, with an OS of 5.65 months. The Burris trial included a frail population, and therefore it can be extrapolated that treatment with GEM is feasible in frail patients.

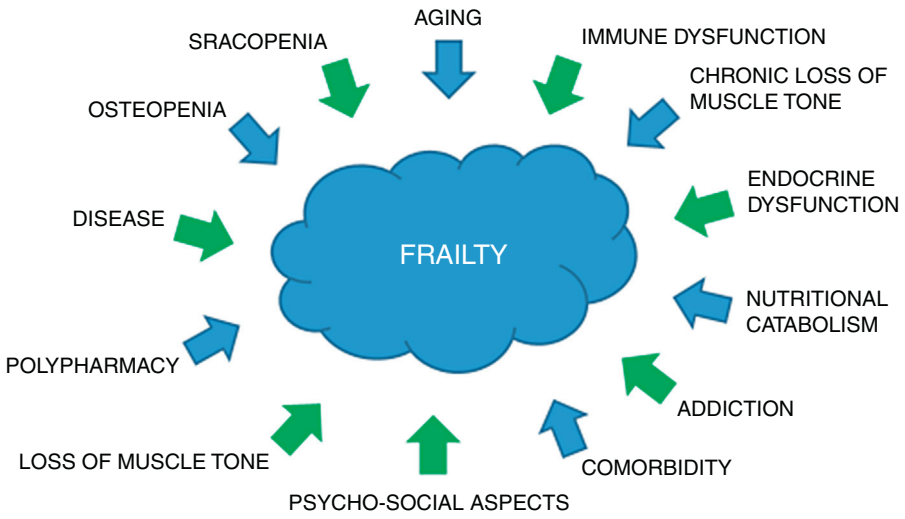


Fig. 1. Factors that contribute to frailty.

1.2.2. MPACT Trial

The MPACT trial compared the combination of GEM + nab-paclitaxel with GEM and showed a statistically significant improvement in OS in favor of the combination of GEM + nab-paclitaxel (8.5 months vs. 6.7 months, Hazard Ratio (HR): 0.72, $p < .001$). PFS and RR were also superior in the experimental arm (5.5 months vs. 3.7 months, HR: 0.69, $p < .01$ and 23% vs. 7%, $p < .001$ respectively) [2]. After the publication of the MPACT trial, GEM and nab-paclitaxel has become one of the standard treatments in the management of mPDAC.

In this study, age was not a limit for enrollment and in fact the median age of patients in each arm of the study was 62 and 63 with an upper limit of 86 and 88 years old, respectively. The percentage of patients with age ≥ 65 years was 41% in the GEM + nab-paclitaxel group and 44% in the GEM group, respectively. In addition, patients with KPS of 70%, which also could be considered frail, were also eligible. Eight percent of patients included in the GEM arm had a KPS of 70%. In addition, in the GEM + nab-paclitaxel arm the percentage of patients with KPS ≤ 70% was 7.4%, including two patients with KPS of 60%.

In a subgroup analysis [16], treatment with the combination of GEM + nab-paclitaxel improved survival both in older patients (defined as ≥65 years) [Hazard Ratio (HR): 0.81 (0.63–1.03)] and in those with poor KPS (70%–80%) [HR: 0.61 (0.48–0.78)]. This suggests that the combination of GEM + nab-paclitaxel is a feasible treatment for frail patients with advanced PDAC, however we have to be cautious due to the low percentage of patients included in the MPACT trial with ECOG 2 or >75 years old.

In addition to efficacy, in frail patients, it is critical to perform a detailed analysis of potential toxicity and impact on quality of life before recommending a specific treatment. In this regard, treatment with the combination of GEM + nab-paclitaxel resulted in an increment in neutropenia, diarrhea, fatigue, and ≥ grade three peripheral neuropathy as compared to GEM alone [16].

An analysis of toxicity by patient subgroups or specific for older patients has not been performed. However, the impact of KPS as a potential indicator of tolerability in frail patients has been studied [17]. The frequency and severity of toxicities of the combination of GEM + nab-paclitaxel were not affected by the KPS at the onset of treatment. In addition, in patients receiving the combination of GEM + nab-paclitaxel, the percentage of dose reductions required were similar in different age groups (40% and 42% for patients <65 and older than 65, respectively) and KPS (42% and 40% for patients with KPS of 90–100 and 70–80, respectively) [18]. These data suggest a similar tolerability between frail patients and the overall population.

It is important to note that dose reductions and treatment delays not only did not negatively impact treatment outcomes but indeed resulted in a significant improvement of OS and PFS in patients for whom the dose was adjusted, likely because a better tolerance allowed longer treatments.

While the MPACT trial indirectly suggested a benefit of the combination of GEM + nab-paclitaxel in patients with low KPS, the small number of patients in this category limited the analysis of efficacy in this patient population. In addition, the study did not explore the safest and most effective dose and schedule of administration in this patient subset. As discussed below, these questions were studied in the recently presented FRAGANCE study [19].

Table 1
PDAC frail patient: Tumor and comorbidity-related signs and symptoms.

Frailty secondary to tumor[a]	ECOG 2 secondary to comorbidity
Signs of malnutrition of cachexia	Severe organic dysfunction
- Weight loss ≥10% in six months - BMI < 18.5 kg/m^2 - Hypoalbuminemia (<3 g/dl) - Diarrhea (malabsorption) - Vomiting, intestinal subocclusion/occlusion	- Neurological dysfuction (severe cognitive dysfuntion) - Endocrine-metabolic dysfuction - Renal dysfunction - Hepatic dysfunction due to prior hepatopathy
Hyperbilirubinemia - Biliary obstruction (choluria, acholia) - Massive hepatic tumor infiltration	HIV or other non-controlled infectious diseases
Incapacitationg pain (epigastric, dorsally irradiated in belt)	Social and psycological issues polimedication
Rapid and progressive clinical deterioration due to tumor progression (depends on baseline disease-free patient status)	Non-controlled psychiatric diseases
Hypercoagulability syndrome, with repeated severe TED episodes	Access to care

[a] TED: Thromboembolic disease; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; HIV: Human immunodeficiency virus.

1.2.3. Accord-11

As the new chemotherapy regimens approved for the treatment of patients with metastatic PDAC are being incorporated into clinical practice, data regarding the efficacy and toxicity of these regimens in frail patients are particularly important. In the ACCORD-11 trial, FOLFIRINOX demonstrated superiority in OS (11.1 vs. 6.8 months, HR: 0.57, $p < .001$), PFS (6.4 vs. 3.3 months, HR 0.47, $p < .001$), and RR (31.6% vs. 9.4%, $p < .001$).

With regards to FOLFIRINOX, observational and retrospective studies have focused on patients who fulfill the eligibility criteria of the phase III trial in terms of Performance Status and age, and there is no available data of efficacy or tolerability with this regimen in frail patients [20]. Currently, administration of FOLFIRINOX is only recommended for patients who fulfill the patient selection criteria as defined in the published study. The PAMELA 70 trial is currently evaluating the efficacy and toxicity of a modified FOLFIRINOX regimen in patients >70 years old [21]. This trial, with a modified FOLFIRINOX regimen, based on pharmacogenetic monitoring of 5-FU and Irinotecan key metabolism enzymes (DPD and UGTA1) to reduce its toxicity, could represent a new treatment option for frail patients with pancreatic cancer.

1.2.4. Fragance Study

Based on the good OS results of the combination of nab-paclitaxel + GEM in patients with metastatic PDAC with KPS ≥70%, the FRAGANCE study was designed to select a tolerable dose -schedule of nab-paclitaxel + GEM (Phase one) and to evaluate the efficacy of the selected regimen (Phase two) in patients with ECOG-2 and previously untreated advanced PDAC [19].

In the phase one portion of the study, patients were randomized to one of four treatment regimens including different doses and schedules of administration of nab-paclitaxel and GEM (Fig. 2).

Every other week schedules of nab-paclitaxel (150 or 125 mg/m^2) plus GEM 1000 mg/m^2 were found to be suboptimal with regards to dose intensity, toxicity, and mortality (30- and 60 day-mortality) and were discarded. Thus, the two regimens selected for phase 2 were nab-paclitaxel (100 mg/m^2, arm C or 125 mg/m^2, arm E) plus GEM 1000 mg/m^2 administered on days one, eight, and fifteen every 28 days). A total of 221 patients were enrolled, 111 in arm C (100 mg/m^2 of nab-paclitaxel) and 110 in arm E (125 mg/m^2 of nab-paclitaxel). Baseline relevant characteristics such as age, gender, and extent of disease were well balanced between the two groups. The most frequent grade 3–4 toxicities reported were anemia (12/7%), neutropenia (32/30%), thrombocytopenia (7/11%), febrile neutropenia (3/4%), asthenia (14/16%), and neurotoxicity (11/16%). When the results achieved in both groups were compared, no significant differences were observed with regards to the primary endpoints. Thus, no significant differences in six month OS (63/69%), RR (24/28%), and median PFS (5.7/6.7 months) were observed, with a median OS of 7.7 (6.3–9.1) (Group C) and 9.8 (7.5–9.8) (Group E) months, respectively ($p = .100$). It was then concluded that the combination of nab-paclitaxel + GEM, at doses of 100 and 125 mg/m^2 respectively, administered on a standard schedule of days 1, 8, and 15 was well tolerated and resulted in acceptable OS, RR, and PFS in this fragile patient population. These results are in agreement with those observed in the MPACT trial [2].

1.3. Randomized Trial beyond gem Progression: Napoli Trial

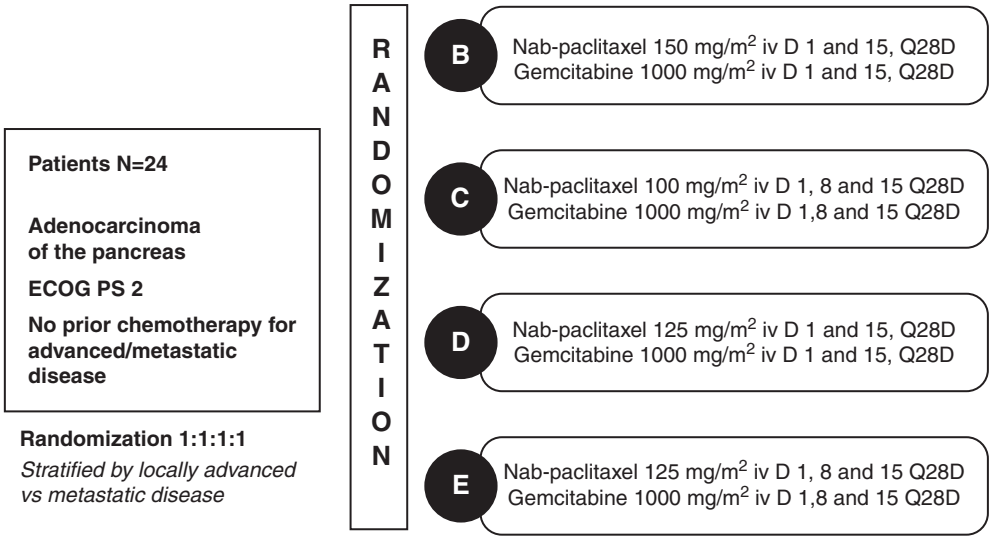
Nal-IRI is a liposomal formulation of irinotecan that was evaluated in a randomized phase III trial (Napoli trial) and demonstrated in combination with 5-fluorouracil a benefit in OS (6.1 vs 4.2 months, HR 0.67, p 0.012), PFS (3.1 vs 1.5 months, HR 0.56, p 0.0001), and RR (16% compared with 1%) [20]. Subgroup analysis demonstrated the same benefit in HR for those patients with better KPS (90–100%) than those with worse KPS (80–70%) (0.79 vs 0.54). Also, patients >65 years benefited from the combination (HR 0.73 in older than 65 years old vs 0.61 in younger patients). However, this combination has some associated toxicity, for this reason we have to consider it with caution in this frail population.

1.4. Outcome of Frail Patients With PDAC in Real Life Data

There are some retrospective trials that have studied the tolerance of GEM monotherapy in patients 70–75 years old or older. The authors concluded in the different analyses that the efficacy and tolerability of GEM monotherapy was the same in both groups [21–24].

There are some reported studies exploring the results of the combination of GEM + nab-paclitaxel in clinical practice. In a retrospective trial published by De Vita et al. in 2016, 26.8% of patients were > 70 years old and 22% had a KPS of 60–70%. Despite these subgroups being over-represented as compared to the MPACT trial, the OS and PFS were 10 and 6.7 months, respectively, which are better than in the pivotal trial. The overall RR was 26% and toxicity was equivalent to the MPACT trial. With regard to prognostic factors, the only variable significantly associated with a reduced OS was a neutrophil/lymphocytic ratio (NLR) > 5 [25].

Giordano et al. analyzed the results obtained with the combination of GEM + nab-paclitaxel in the first line setting in an unselected group of patients with advanced PDAC [26, 27]. The results showed a median OS of eleven months, median PFS of seven months, and 28% partial responses. No differences in outcome were noted in patients



*D: Day; Q28D: Evert 28 days; ECOG PS: Eastern Cooperative Oncology Group Performance Status; iv: intravenous

Fig. 2. Fragance study: design of phase 1 of the study [19].

>70 years old, who represented 35% of the studied patients. Patients with a NLR > 5 and ECOG 2 had worse survival in the univariate analysis but not in the multivariate analysis. In a second analysis of 145 patients with advanced PDAC treated at eighteen centers in Italy with the same regimen, no significant differences in outcome were observed in the subgroups of patients >75 years old (15.4%), ECOG two (16.9%) or with a biliary stent (21.2%). Similar to the results observed in the MPACT trial, 25–30% of patients required a dose reduction. Older patients developed more reversible neurological toxicity but less hematological toxicity [28, 29].

Regardless of data with FOLFIRINOX in older patients, some retrospective data suggest it can be used with caution in patients >70 years old [30]. There are some retrospective data showing that older mPDAC patients treated after 2010 were more likely to receive multiple chemotherapeutic agents compared to older patients treated prior to 2010. These interventions were associated with a small survival advantage. Although these results are in line with the standard of care, the small OS advantage and significant toxicity profile of these treatments warrant further research to optimize the treatment of older patients with mPDAC [6].

One option to treat frail patients is to use a modified GEM and nab-paclitaxel schedule. Dr. Krishna presented a retrospective analysis of a prospectively established database of patients who received the modified regimen with GEM and nab-paclitaxel (days 1 and 15 of a 28-day cycle). Sixty-three patients were evaluable for toxicity, and 47 were evaluable for response. Patients on the modified regimen had a PFS of 4.8 months and median OS of 11.1 months. With the modified regimen, 27% of patients experienced neurotoxicity of any grade, with the rate of grade 3 or 4 toxicity <2%. The rate of grade 3 or 4 neutropenia was 10% [31]. Nevertheless, the results should be cautiously evaluated since this is a single institution retrospective study.

1.5. Management Recommendations Based on Guidelines

Table 2 summarizes the recommendations for the management of frail and/or older patients with advanced PDAC issued by professional societies and experts groups. Notwithstanding differences among the various guidelines, frail patients should be offered palliative treatment with either GEM + nab-paclitaxel or GEM monotherapy. No age restriction is recommended to receive chemotherapy except that patients >75 years old should not be treated with FOLFIRINOX.

Our group published the GALLgo classification in 2016 that proposes a practical classification for the management of these patients [10]. Briefly, three groups were defined: Patients with no restrictions for chemotherapy include those with PS 0–1, age ≤75 years, bilirubin ≤1.5 ULN, good nutritional status, and no comorbidities. These patients are candidates for treatment with the combination of GEM + nab-paclitaxel or FOLFIRINOX. Patients with limitations for the use of chemotherapy include those with at least one of these factors: age > 75 years, ECOG two, mild to moderate organ dysfunction, bilirubin >1.5 ULN (when obstructive causes have been resolved), recent cardiovascular comorbidity, or moderate nutritional deficits. In these patients and especially in those with a high tumor burden, the combination of GEM + nab-paclitaxel is the preferred treatment option. However, if there are multiple comorbidities, single agent GEM can be also considered. Finally, patients with ECOG three-four or those with severe organ dysfunction are best served with palliative symptomatic treatment, although some selected patients with ECOG three with a heavy tumor load could benefit from systemic chemotherapy.

1.6. Symptomatic Treatment of Frail Patients With Advanced PDAC

In this section we will focus on the principal and more frequent symptoms observed in patients with advanced PDAC as well as the recommended management for this specific patient group. The most common complications of PDAC are due to tumor growth and invasion of adjacent organs (bile duct and duodenal obstruction, exocrine and endocrine pancreatic insufficiency, and pain) as well as systemic events such as cachexia and thromboembolic events. There are other complications not related to tumor growth, such as psychological symptoms (anxiety and depression). The establishment of early treatment of these symptoms in a multidisciplinary setting is crucial.

1.6.1. Pain Management

>75% of the patients present pain, mostly due to infiltration of the celiac plexus, at some point during their medical course [32]. It is recommended the use of pharmacological treatment, emotional support, health education and close supervision of drug induce side effects, regardless of the intensity of the pain (GALLgo guidelines) [10].

Currently, the WHO pain scale is still recommended despite being centered in pain intensity and not in the cause and characteristic of

Table 2
Recommendations of different Medical Societies and Expert Panel for the management of frail and/or older patients with advanced PDAC [8–14].

	Oettle et al. [8]	GALLgo [9]	ESMO [10]	SEOM [11]	NCCN [12]	ASCO [14]
Frail patients[a]	CT with gemcitabine as standard of care in PS 2 GEM + nab-paclitaxel in selected PS 2 cases (not if neuropathy)	PS 2: GEM + nab-paclitaxel (High tumor burden) vs GEM (comorbidities) PS 3–4: Palliative treatment In selected PS 3 secondary to tumor load, CT can be considered	PS 3–4: no CT PS 2, if need of high response, GEM + nab-paclitaxel PS 2 or bilirubin >1.5 x ULN, GEM	Frail patients defined with comorbidities, mental health status and support, fatigue, polypharmacy and geriatric syndromes ECOG >2 or frail patients: no CT ECOG 2 or fit patients ≥75 years: GEM vs GEM + nab-paclitaxel	Poor PS defined as PS > 1 or poor nutritional status or not patent biliary stent or poor pain control Poor PS: GEM or GEM + nab-paclitaxel (if KI ≥ 70%) or palliative treatment	ECOG 2: GEM and can add capecitabine or erlotinib ECOG 3: Palliative treatment
Older patients	Age not specified per se in order to choose CT	Age not specified per se in order to choose CT except that elderly patients (>75) should not receive FOLFIRINOX	Age not specified per se in order to choose CT	Age not specified per se in order to choose CT except that elderly patients (>75) should not receive FOLFIRINOX	Age not specified per se in order to choose CT	Not specified
Other practical considerations	Increased risk of febrile neutropenia and neurotoxicity with GEM + nab-paclitaxel in frail and/or elderly patients Consider prophylactic G-CSF or dose reduction in ≥70 years	Nutritional assessment recommended in all patients Geriatric assessment recommended in >70 years-old. Consider dose reduction of GEM + nab-paclitaxel if elevated bilirubin		Geriatric assessment recommended in >70 years-old.	Patient factors must be taken into account (PS, age, comorbidities and frailty)	Not specified

[a] CT: Chemotherapy; ESMO: European Society of Medical Oncology; Gallgo: Grupo Multidisciplinar de Expertos para el desarrollo de un algoritmo de tratamiento en Cáncer de Páncreas; NCCN: National Comprehensive Cancer Network: PS: Performance Status; SEOM: Sociedad Española de Oncología Médica; ULN: Upper Normal limit; ASCO: American Society of Clinical Oncology; FOLFIRINOX: Combination of 5- Fluorouracil+ leucovorin + irinotecan + oxaliplatin; G-CSF: Granulocyte colony stimulating factor.

the pain. For patients with minimal pain, the current recommendation is to use nonsteroidal anti-inflammatory drugs (NSAIDs) considering maximum recommended doses as well as associated side effects such as gastrointestinal bleeding or kidney injury [33]. For patients with moderate or severe pain, opioids are considered the first line for management of visceral cancer pain, including that cause by PDAC [34]. In this patient population, it is important to carefully monitor the doses used as well as possible interactions with other drugs (particularly in patients with chronic diseases that require additional medications). An option to reduce the use of opioids is to perform a celiac plexus block, a strategy that is effective in controlling pain in up to 80% of patients, with a median duration of three months [35].

1.6.2. Management of Biliary Obstruction

Up to 70% of patients with PDAC present with bile duct obstruction that, if left untreated, leads to rapid deterioration of patient overall health status [36]. Most guidelines recommend a metal stent placement by endoscopy (preferred to transhepatic percutaneous placement, which is associated with a higher degree of complications). For patients with expected survival of less than four months, a plastic stent is also a less expensive alternative [37]. However, some studies suggest that age may be a poor prognostic factor in relation to permeability when a plastic stent is chosen.

1.6.3. Management of Duodenal Obstruction

Approximately 20% of patients present with duodenal obstruction. For patients who undergo attempted surgical resection and are deemed to be unresectable, a gastrojejunostomy is a safe and effective approach. As recommended in the GALLgo guidelines, an expansible metallic duodenal prosthesis is very efficacious with a 96% technical success rate and 90% clinical success rate. Complications include re obstruction, migration, perforation, and bleeding, but the risk of serious (1%) or minor (26%) complications is very low [38].

1.6.4. Cachexia

Tumor cachexia is a multifactorial syndrome that may affect more frail patients. It is characterized by a permanent loss of skeletal muscle mass (with or without fat loss) that cannot be corrected with conventional nutritional support [39]. Currently, there is no effective treatment for this condition. According to the GALLgo guidelines, there are two drugs approved for cancer related anorexia (megestrol acetate and high dose steroids). Neither one is exempt from potential serious side effects and should be used cautiously and on an individualized manner [40].

1.6.5. Exocrine Pancreatic Insufficiency

The prevalence of exocrine pancreatic insufficiency (EPI) is estimated to affect more that 50% of patients with advanced PDAC, being more common in patients with a prior surgical resection [41]. The diagnosis is usually clinical, as patients present with steatorrhea. EPI is a risk factor for malnutrition and vitamin deficit. If clinical EPI is suspected or EPI diagnosis is confirmed, substitute treatment with Pancreatin (Kreon®) should be initiated at a dose of least 25,000–50,000 U with each meal. Low fat diets are not recommended [41].

1.6.6. Thromboembolic Disease

Thromboembolic disease (TED) is one of the most frequent complications in patients with PDAC, with an incidence of 20 to 35% [42]. The etiology is multifactorial and involves general as well as tumor specific factors. The routine use of prophylaxis for TED is not recommended in ambulatory patients due to the variable risk, bleeding potential, and unclear results from clinical trials. However, it is recommended to periodically evaluate the risk, discuss symptoms and potential risks with the patient, and consider using prophylaxis with low molecular weight heparin (LMWH) in patients with high risk of TED (Khorana index ≥3) without risk of bleeding. These patients require close monitoring [43].

With regards to patients with low bleeding risk, the metaanalysis of Ben-Aharon et al., that included the results of CONKO-004 and FRAGEM-UK studies, showed a significant reduction of Venous Thromboembolism (VTE), with a RR of 0.31% (95% CI: 0.18–0.55), with no significant increase in major bleeding events or overall survival [44]. This data, together with the results of CONKO-004 and FRAGEM-UK studies, have led to the establishment of the following international guideline for patients with low bleeding risk: Primary pharmacological prophylaxis of VTE with LMWH is indicated in patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 1B) [45].

1.6.7. Psychological Support

PDAC can have an enormous psychological toll on those affected by it [46]. The knowledge of the aggressive nature the disease may lead to depression and anxiety in patients affected, even at the early course of the disease. For that reason, patients should have a full assessment of symptom burden, psychological status, and social supports as early as possible, preferably at the first visit (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong) [14]. All patients can benefit from a discussion of their psychosocial concerns and their available support system, including palliative care. Some patients may require treatment with antidepressants or anxiolytics, and others may need referral for ongoing formal support from a social worker, psychologist, or psychiatrist [14]. Referral to palliative care services will help patients and relatives to be able to get answers for questions beyond specific disease treatment. The physician should always clarity that the use of such services is not synonymous with a referral to hospice care [14].

2. Conclusions

The frail patient population represents a very important percentage of patients diagnosed with PDAC and is currently understated in clinical trials. A high percentage of patients with advanced PDAC are older and a geriatric assessment is recommended in these patients. From the results of the MPACT trial, it can be inferred that, although the percentage of frail patients was small, the combination of GEM + nab-paclitaxel was the preferred treatment for this subgroup of patients. The results of the recent FRAGANCE study show that the combination of nab-placlitaxel + GEM, at doses of 100 and 125 mg/m^2, respectively, administered on a standard schedule of days one, eight, and fifteen, is the recommended schedule for the frail subpopulation. With regards to recommendations based on current clinical guidelines, frail patients should be offered palliative treatment with either the combination of GEM + nab-paclitaxel (high tumor burden) or GEM monotherapy (comorbities). No age restriction is recommended to receive chemotherapy except that patients >75 years old should not be treated with FOLFIRINOX. It is also recommended to add palliative treatment for the management of symptoms and systemic events related to tumor growth (pain, biliary/duodenal obstruction, cachexia and exocrine pancreatic insufficiency, and thromboembolic disease).

Conflict of Interests

The authors declare to have no conflict of interest.

Authors Contributions

All authors have contributed to: Study concepts, study design, data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation, manuscript editing and manuscript review.

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