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Tumour Review

Chemotherapy in elderly patients with pancreatic cancer: Efficacy, feasibility and future perspectives

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ABSTRACT

By 2030 70% of newly diagnosed pancreatic ductal adenocarcinoma (PDAC) will occur in older adults. Elderly patients, defined by the World Health Organization (WHO) as people older than 65 years, represent a heterogeneous group with different biological and functional characteristics that need personalized anticancer treatments. Since older patients are under-represented in randomized phase III trials, their management is mostly extrapolated from studies performed in younger patients, without robust evidence-based recommendations. However, data from retrospective studies and case-control series show that elderly may benefit from chemotherapy in both the adjuvant and advanced disease settings. Although with discordant results, gemcitabine-based treatment and dose-adapted fluorouracil combination regimens seem to be effective and well tolerated in this subset of patients.

A proper balance of potential treatment benefits and side effects represent the crucial point for managing elderly patients with PDAC. Therefore an appropriate patient selection is essential to maximize the therapeutic benefit in the older population: randomized studies aiming to better standardizing fitness parameters and implementing the routine use of comprehensive geriatric assessments are strongly warranted. In this light, the detection of molecular prognostic markers able to detect patients who may benefit more from oncological treatments should be a primary endpoint of age-focused clinical trials. Altogether, the field of geriatric oncology will expand in the next years, and the clinical management of elderly patients affected by PDAC will become a major public health issue.

Introduction

The global population aging is currently defining a new class of oncological patients, with their own special characteristics and needs. According to the WHO 65 years is the established cut-off to define people as 'elderly', but strict application of age ranges fails to properly label older adults since ageing is an highly individualized process, based on genetics, lifestyle and overall health, and the potential discrepancy between chronological or biological age increases over the years [1,2]. The population aged 60 or more will double worldwide by 2050, and those aged 80 or more will number about 400 million people [3]. In the light of the well-established age-cancer association, the number of old people affected by cancer will rapidly increase, representing the prototypical cancer patients of the near future.

As for many other cancer types, the incidence of PDAC increases with age, raising the highest peak after 60 years. By 2030, approximately 70% of PDAC will be diagnosed in older adults [4]. In 2014 pancreatic cancer deaths were about 22.000 in patients aged from 60 to 79 years, and 11.800 in people over 80, corresponding to about 54% and 30% of the total deaths in the two age-ranges, respectively [5]. It would be tempting to conclude that age were the most important prognostic factor in PDAC, but data show that older age itself is not enough to define poor prognosis: survival in young and old patients is similar when performance status is poor at diagnosis or when disease onsets at a very advanced stage [6–9]. Despite recent advances in PDAC treatment, management of elderly patients is still a challenge, mostly due to the lack of information on safety and efficacy of chemotherapy from clinical trials, in which old patients are under-represented.

The low proportion of elderly adults enrolled in clinical trials has been underlined for the first time comparing the number of elderly cases involved in registration studies from 1995 to 2002 at the US Food and Drug Administration (FDA), and the estimated number of elderly patients affected by same cancer type and stage in the US population. Overall, patients aged 65 years or more represented 36% of the study

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population as compared with 60% of the US cancer population, whereas the enrollment of patients aged 70 or 75 and more were 20% and 9% respectively in trials, compared with 46% and 31% of same-age and same cancer-type population. Two of the 55 studies of FDA involved PDAC patients, still confirming the increasing discrepancy between patients enrolled in prospective studies (< 40%) and the real cancer incidence in older age (70% of same–age PDAC patients in the general population) [10]. The updated analysis of registration trials from 2007 to 2010, including the erlotinib study for advanced PDAC, showed once again that only 33% of patients aged 65 or more were included, while 59% is the same-age cancer population [11,12].

More recently, the expansion of immunological treatments for solid tumors, to which PDAC will surely be candidate [13], has focused the attention on age-related dysregulation of the immune system and increased pro-inflammatory milieu. Besides that, the number of elderly enrolled in phase III trials leading to FDA approval of immune checkpoint inhibitors was limited, with uncertain benefit in term of overall survival (OS) in the older subpopulation. For these reasons the ELDERS study was launched in 2016 to assess the efficacy, safety and impact on quality of life of immunotherapy when given to elderly patients in comparison with a young population [14,15].

Adjuvant chemotherapy in resected PDAC elderly patients

The beneficial role of adjuvant chemotherapy was repeatedly demonsrated in patients with resected PDAC independently of age. Chemotherapy after surgery has increased the overall 5-yrs OS in PDAC patients from 10% to about 25% over the years, according to individual studies studies [16–23] (Table 1).

The CONKO-001 and ESPAC-1 trials proved that gemcitabine or 5-fluorouracil improved OS and disease-free survival (DFS) compared to surgery alone [16,17]. Furthermore, the ESPAC-3 and the RTOG 97-04 trials showed that gemcitabine and fluorouracil led to similar benefit in the adjuvant setting when directly compared [18,19], albeit the JASPAC-01 trial showed superiority of the fluoropyrimidine prodrug S1 over gemcitabine in Asiatic population. The Japanese population seems to benefit from S-1 (tegafur) more than gemcitabine after PDAC resection, with a 5-years OS of 44% vs 24% respectively ($p < 0.0001$) and independently by age [20]. Of interest, a small retrospective study investigating the safety and feasibility of adjuvant S-1 in Asian patients ≥ 70 showed that, even without a statistically significant difference, the treatment continuation rate at 6 months was similar in elderly when compared to younger patients (72.7% vs 60.5% respectively; $p = 0.35$). Even if OS data were missing, the analysis suggested a good tolerability and feasibility of adjuvant S-1 in the older population [21]. More recently, the ESPAC-4 trials has suggested that the gemcitabine-capecitabine combination may offer some survival benefit as compared to single agent gemcitabine (median OS 28 months versus 25.5 months). Noteworthy, in all the studies patients aged ≥ 65 years had survival benefit similar to younger patients, but no information about patients > 75 was provided [16–23].

Several retrospective analyses have assessed the role of adjuvant chemotherapy in the subset of elderly patients. The Australian Pancreatic Cancer Genome initiative analyzed 439 patients with resected PDAC from 1990 to 2011, showing that people older than 70 (40% of the study population) were less likely to receive adjuvant treatment in comparison to the younger population (51.5% vs 29.8% respectively, $p < 0.001$). Moreover, not receiving chemotherapy was an independent prognostic factor for poor OS in the elderly subpopulation (HR: 1.89; CI: 1.27–2.78; $p = 0.002$). Patients ≥ 70 who received adjuvant treatment had a survival benefit of the same magnitude of younger patients (21.8 vs 22.5 months), received the same number of cycles of chemotherapy (average 5), which mostly consisted of gemcitabine (79%) [23].

Altogether, data on the efficacy of adjuvant chemotherapy in resected PDAC, seem to support the administration of a post-surgery treatment for eligible patients with good PS, whatever their age [24]. However, lack information about treatment-related toxicities in older patients makes it difficult to weight the balance between potential benefit and side effects from adjuvant chemotherapy. Moreover, since the elderly population includes patients ≥ 65 up to 80 and more, one can argue that people > 75 might benefit less from treatments when

Table 1
Selected studies on adjuvant chemotherapies.

Trial	Type of study	N	Time frame	Age range	Treatment	Primary endpoint	Results (months)	HR – (95% CI)	p-Value
Oettle (2013), CONKO-001 [16]	R, phase 3	354	1998–2004	34–82 ≥65: 61% > 75: n.n	GEM vs OBS	DFS	13.4 vs 6.9	0.55 [0.44–0.69]	< 0.001
Neoptolemos (2004), ESPAC-1 [17]	R, phase 3	289	1994–2000	IQR:54–67 ≥65: n.n > 75: n.n	5FU/FA vs OBS	OS	20.1 vs 15.5	0.71 [0.55–0.92]	0.009
Neoptolemos (2010), ESPAC-3 [18]	R, phase 3	1088	2000–2007	31-85 IQR:59–69 ≥65: n.n > 75: n.n	5FU/FA vs GEM	OS	23.0 vs 23.6	0.94 [0.81–1.08]	< 0.39
Regine (2008), RTOG 97-04 [19]	R, phase 3	451	1998–2002	33–84 ≥65: n.n > 75: n.n	CRT + GEM vs CRT + 5FU	OS	20.5 vs 17.1	0.84 [0.67–1.05]	0.12
Neoptolemos (2017), ESPAC-4 [22]	R, phase 3	730	2008–2014	37–81 ≥65: 47% > 75: n.n	GEMCAPE vs GEM	OS	28.0 vs 255.5	0.82 [0.68–0.98]	0.032
Uesaka (2016), JASPAC 01 [20]	R, phase 3	385	2007–2010	53–73 ≥65: 60% > 75: n.n	GEM vs S-1	OS	25.5 vs 46.5	0.57 [0.44–0.72]	< 0.0001
Nagrial (2013), [23]	Retrospective	439	1990–2011	28–87 < 70: 59.5% ≥70: 40.5%	CHEMO vs OBS	OS	≥ 70: 21.8 vs 13.1	n.n	0.003
Aoyama (2015), [21]	Retrospective	76	2007–2014	46–81 < 70: 46% ≥70: 54%	S-1	6-mo CR	< 70: 60.5% ≥70: 72.2%	n.n	0.35

N: number of evaluated patients; R: randomized; vs: versus; GEM: gemcitabine; OBS: observation; DFS: disease free survival; IQR: interquartile range; 5FU/FA: fluorouralcil and folinic acid; OS: overall survival; CRT: chemo-radiotherapy; GEMCAPE: gemcitabine and capecitabine; S-1: tegafur; 6-mo CR: 6 months-continuation rate.

Table 2
Selected studies on locally advanced or metastatic PDAC.

Ref	Study	N	Age range	Time frame	Treatment	Primary Endpoint	Results	HR (95% CI)	p-value
Kuroda (2017) [26]	Retrospective	895	33–98 < 65: 26% ≥65: 74% > 75: n.n	2001–2010	CHEMO vs BSC	% BSC patients	< 65: 25.8% ≥65: 47.8%	n.n	0.001
Yamagishi (2010) [27]	Retrospective	66	36–86 < 70: 47% ≥70: 33% > 75: 28% BSC: 19%	2000–2007	GEM vs BSC	OS	< 70: 10.3 mo ≥70: 9.7 mo BSC: 4.2 mo	n.n	0.05
Marechal (2008) [7]	Retrospective	99	< 70: 57.5% ≥70: 42.5%	2001 –2004	GEM-based CHEMO	OS	< 70: 240 days ≥70: 220 days	n.n	0.88
Hentic (2011) [28]	Retrospective	38	75–84	2000–2006	GEM/GEMOX vs BSC	OS	9.1 vs 2.9 mo	n.n	n.n
Locher (2008) [29]	Observational	39	70–82	1999–2004	GEM	Toxicity, RR	NEU-G3/4: 38% DCR:43.6% OS:10 mo 1yOS: 30%	n.n	n.n
Van der Geest (2017) [37]	Retrospective	9047	< 70: 50% 70–74: 17% 75–79: 15% ≥80: 17%	2005–2013	CHEMO vs BSC	OS	< 70: 26 vs 12 w 70–74: 27 vs 11 w 75–79: 20 vs 11 w ≥80: 16 vs 10 w	< 70: ref. 70–74: 0.92 75–79: 1.21 ≥80: 1.48	< 70: 0.001 70–74: 0.001 75–79: 0.001 ≥80: 0.02
Kadokura (2016) [30]	Retrospective	67	75–90	2006–2014	GEM and/or S-1 vs BSC	RR, OS	DCR: 55.2% OS: 9.2 vs 1.7 mo	n.n	0.001
Conroy (2011) [33]	R, phase 3	342	< 65: 71% ≥65: 29%	2005 –2009	FOLFIRINOX vs GEM	OS	11.1 vs 6.8 mo	0.57	0.001
Van Hoff (2013) [34]	R, phase 3	861	< 65: 58% ≥65: 42%	2009–2012	AG vs GEM	OS	8.5 vs 6.7 mo	< 65: 0.65 ≥65: 0.81	0.001
Guion Dusserre (2016) [35]	Retrospective	18	70–87	2009–2015	FOLFIRINOX	OS	12.5 mo	n.n	n.n

N: number of evaluated patients; R: randomized; GEM: gemcitabine; BSC: best supportive care; GEMOX: gemcitabine and oxaliplatin; RR: respone rate; NEU-G3/4: neutropenia G3-G4; DCR: disease control rate; OS: overall survival; 1yOS: one year overall survival; S-1: tegafur; vs: versus; ref: reference; w: weeks; mo: months.

Table 3
Selected geriatric scales.

	fTRST		G8		VES-13	
PARAMETERS						
	Cognitive impairment	0–2	Food intake decline in past 3 months	0–2	Age	1–3
	Living alone	0–1	Weight loss in last 3 months	0–3	Self-consideration on health status	0–1
	Difficulty in mobility in the past 6 months	0–1	Mobility	0–2	Difficulty on physical activities	0–2
	Hospitalization in the last 3 months	0–1	Neuropsychological problems	0–2	Difficulty in every-day activities	0–4
	Polypharmacy (> 5 medications)	0–1	BMI	0–3		
			Medications (≥3/day)	0–1		
			Self-consideration on health status	0–2		
			Age	0–2		
SCORE RANGE	0–6		0–17		0–10	
ABNORMALITY	≥2 (in oncologic patients ≥ 1)		≤14		≥3	
TIME	2 min		5 min		5 min	
SENSITIVITY	92% (cut-off ≥ 1)		65–92%		39–88%	
SPECIFICITY	42% (cut-off ≥ 1)		3–75%		62–100%	

Ftrst: Flemish version of the Triage Risk Screening Tool; VES-13: Vulnerable Elders Survey-13; BMI: Body Mass Index; min: minutes.

compared to patients 65–70 years old, with a higher rate of side effects due to increased frailty.

Chemotherapy in locally advanced and metastatic PDAC elderly patients

A number of retrospective, post-hoc and subset analyses investigated whether age itself might influence survival, or predict efficacy and tolerability of chemotherapy in advanced pancreatic cancer, raising several issues and unanswered questions on management of the elderly population (Table 2).

Elderly patients are not only under-represented in clinical trials, they also seem to receive standard chemotherapy less often than younger patients [25]. A multicenter review of 895 unresectable PDAC patients highlighted the under-treatment trend for people older than 65 years in comparison to younger ones, with a proportion of 52% and 74% of patients receiving chemotherapy, respectively. No difference in OS was found between the old and younger subgroup when treated (274 vs 333 days, $p = 0.09$), either with gemcitabine or fluorouracil-based chemotherapy. Consistently, more elderly patients were assigned to receive BSC when compared to young patients (48% vs 26%, $p \leq 0.001$), still with similar OS between the two groups (84 vs 78 days, $p = 0.83$). Among patients in the BSC group, 51% of elderly actually met the eligibility criteria for chemotherapy. They received BSC because they were not properly informed of their diagnosis, or they were treated according to their family preferences, or to the physicians' policy for this age group [26]. Irrespective of the limitations of the available data, the information rises concerns for the number of elderly

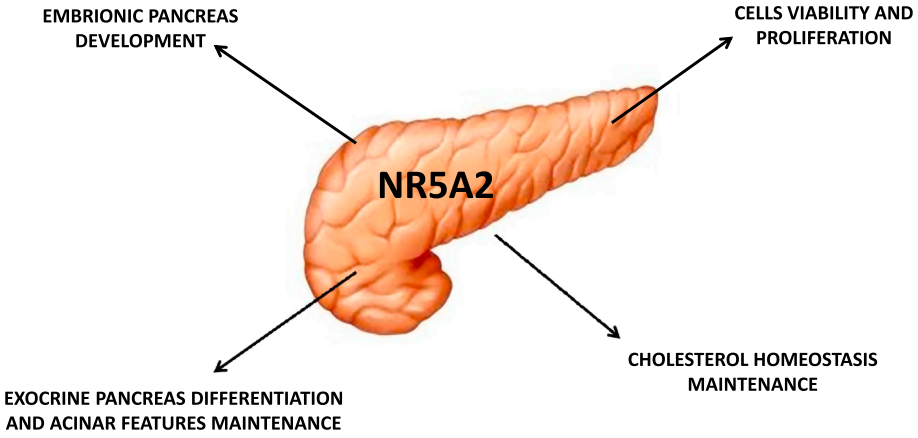

Fig. 1. NR5A2-driven processes in exocrine pancreas.

patients recommended for BSC without being properly informed on the prognosis and therapeutic options based on beliefs about disease and chemotherapy worthwhileness.

With regard to chemotherapy, gemcitabine showed antitumor activity in elderly patients affected by locally advanced and metastatic PDAC in several studies [7,27–29]. A small Japanese study, in which dose reduction was significantly more frequent in patients aged ≥ 70 years due to hematological toxicity, showed that survival rate was not influenced by side effects, when compared gemcitabine and BSC in elderly and younger patients, with an OS of 311 and 292 days respectively [27]. Similar results were gained by gemcitabine-based regimens in patients ≥ 70, confirming that performance status is the major prognostic factor in both old and young patients [7].

Another Japanese trial confirmed the efficacy of gemcitabine and S-1-based chemotherapy in old and young PDAC patients (mOS 9.2 vs 10.2 months, respectively). In addition, the authors identified neutrophil-lymphocyte ratio (NLR) as a potential prognostic factor able to identify elderly patients who benefit more from chemotherapy [30]. Further evidence is endorsing the use of NLR in PDAC as a valuable prognostic marker to select elderly patients for active treatment or BSC [31,32].

Recently, FOLFIRINOX and nab-paclitaxel-gemcitabine increased OS of metastatic PDAC over single agent gemcitabine in two phase III trials [33,34]. The PRODIGE-4/ACCORD-11 trial enrolled patients aged up to 76 years, but only 28% of the trial population was older than 65 years. Unfortunately, data about safety in the elderly population were missing [33]. Conversely, a retrospective monocentric study analyzed 52 patients aged ≥ 70 treated with FOLFIRINOX for histologically proven pancreatic (n = 18) or colorectal cancer (n = 34). The study had several limitations, including the evaluation of PDAC patients in both stage III and IV regardless of number and kind of treatment received before, altogether providing a median OS of 12 months in the pancreatic cohort. Major toxicities were neutropenia in 33% of cases (58% of whom with grade 4) and diarrhea in 67% of the whole population (14% grade 4), in both cohorts. Finally, 75% of patients were treated with reduced doses of chemotherapy form the beginning and 27% had a dose-adjustment during treatment, making it difficult to understand the true feasibility of this regimen in the pancreatic cohort [35]. To properly assess the efficacy and the tolerability of dose-adapted FOLFIRINOX regimen in patients aged 70 years or more, the PAMELA-70 trial is enrolling chemo-naive elderly cases with metastatic PDAC since 2014 [36].

In the MPACT study 42% of patients were 65–88 years old. Keeping in mind the limitations of a post-hoc analysis on a subset of patients, it still ids of interest that the hazard ratio for disease progression was 0.69 (0.52–0.91) for both young and older patients, while hazard ratio for overall survival was 0.65 (0.53–0.79) for patients < 65 but only 0.81 (0.63–1.03) for those older than 65. This MPACT results reported an overall acceptable toxicity even if, once more, data were not stratified by age [34].

A recent retrospective study suggested that very old age itself seems to be associated with poor OS in treated patients. The Netherlands Cancer Registry Study enrolled 2180 patients with primary metastatic PDAC receiving palliative chemotherapy. The study population was divided in four age groups: < 70; 70–74; 75–79; > 80 years. Each group benefited by chemotherapy compared to the same-age untreated patients: 26 vs 12 weeks in younger than 70; 27 vs 11 weeks from 70 to 74 years; 20 vs 11 weeks for patients up to 79 (all $p < 0.001$); and 16 vs 10 weeks in older than 80 ($p = 0.02$). The findings seem to suggest that the treatment-related survival benefit is inversely correlated with age being 26–27 weeks in people younger than 74 years, 20 weeks from 75 to 79 years, and only 16 weeks in patients ≥ 80 ($p = 0.003$). Each group of older patients showed a worse OS than the chemo-treated patients younger than 70 (75–79 vs < 70 HR 1.21, C.I:1.02–1.44; ≥ 80 vs < 70 HR:1.48, C.I: 1.06–2.07) except for the intermediate age group (70–74 vs < 70 HR 0.92, C.I:0.81–1.03). Even if the rate and type of comorbidities increased in very old patients, comorbidity did not emerge as related to poor prognosis in multivariate analysis [37].

In conclusion all the above studies emphasize the remarkable relevance of a proper selection of old patients for chemotherapy, highlighting the need of reliable prognostic markers to drive the treatment-decision process.

Instruments for patients selection. From geriatric scales to molecular medicine

In medical practice, treatment decision for patients with locally advanced or metastatic PDAC mostly relies on individual clinical judgment, mainly based on Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status scales. When considering older people, clinical judgment might be biased by an overestimation of the fitness of patients or by using age as a surrogate of comorbidity, vulnerability and susceptibility to chemotherapy adverse effects [38,39]. Scales of performance status are poorly reliable for old cancer patients, since relevant information, such as polypharmacy, comorbidities, functional status or family support, are not taken into account [40,41]. To improve the decision-making process for old cancer patients the International Society of Geriatric Oncology recommend the performance of a comprehensive geriatric assessment (CGA), which represent the most appropriate method to obtain a global appraisal of the health status of old individuals, including social situation, functionality, falls, cognitive and mood changes, nutritional status [42]. Despite multiple studies have shown that CGA can predict cancer-related mortality and chemotherapy related-toxicities, its integration in clinical practice is not implemented due to its time and resource-consuming nature. As an alternative to CGA, a number of screening tools

has been proposed to help physicians identifying frail patients (Table 3). Among those alternative approaches, the highest sensitivity in older cancer patients was provided by G8 (> 80%) and fTRST (> 90%) scales [39,40]. While the use of screening tools might be helpful to optimize treatment selection for the elderly, their routine application is not fully integrated in all oncology practices, and multidisciplinary geriatric oncology studies are needed to better standardize their use.

Besides the primary role of a better standardization of fitness parameters in the elderly, the detection of reliable prognostic markers in order to select older patients for chemotherapy still remains an unmet need. In this perspective, molecular medicine may offer an opportunity, even if the PDAC molecular complexity becomes even more challenging when looking for age-related markers. The pancreatic landscape of high intra and inter tumor heterogeneity is revealed by the ubiquitous KRAS mutation, the onco-suppressor genes inactivation, but mostly by the number of genes mutated at low and individual prevalence, proving the remarkable heterogeneity of mechanisms involved in pancreatic cancer carcinogenesis, regardless of the age of the disease onset [43–45].

Previous studies showed a large patho-morphological and molecular overlap between elderly and young PDAC patients, postulating an increased p53 protein expression in old PDAC people or a greater incidence of mucinous and adeno-squamous histotype, as well as the low rate of KRAS mutations in younger patients [46–48].

Recently, six single nucleotide polymorphisms (SNPs) related to blood lipid levels were found to be associated with PDAC development in elderly Japanese patients. In particular SNPs in the NR5A2 gene region (nuclear receptor subfamily 5 group A member 2, also known as LRH-1) were associated with increased PDAC risk [49], as already proven by integrated genomic analysis [44,50].

NR5A2 gene encodes for a nuclear receptor protein expressed in undifferentiated embryonic stem cells. Its expression is needed for the developing pancreas and for the maintenance of acinar features in the exocrine gland, suggesting a specific role of NR5A2 in the prevention of inflammation-induced acinar-to-ductal metaplasia, acting through the maintenance of differentiation-specific functions, as recently showed by Cobo and colleagues [51] (Fig. 1). Moreover NR5A2 gene is implicated in a variety of biological processes, including cell viability [52] proliferation [53] and cholesterol homeostasis: in the exocrine pancreas NR5A2 induces the expression of carboxyl ester lipase, which is involved in the absorption of cholesteryl esters and the assembly of lipoproteins by the intestine, regulating the blood cholesterol level availability [54,55]. Taken together, the altered function of NR5A2 in older patients with PDAC might induce a defective regenerative response to damage, fostering inflammatory process, together with enhancing the lipid-associated metabolic pathways, by which PDAC cells proliferation is highly dependent [56]. The excitement about NR5A2 gene is justified because it is a druggable target and has potential application in the growing population of elderly patients, and might well cooperate in decreasing PDAC onset and progression [57,58].

Since abnormality in lipid metabolism and increased cholesterol level is growing with age, it seems reasonable that a recent meta-analysis of PDAC patients, collected from the Surveillance, Epidemiology and End Results (SEER) Medicare Registry that include the 97% of US people ≥65, showed an improved OS for patients treated with statins in comparison with non-users. In particular, post-diagnosis use of statins reduced the mortality risk of about 30% when compared to non-users, regardless of disease stage and treatments [59]. A previous SEER-analysis also indicated that simvastatin is associated with enhanced survival among patients ≥65 affected by early-stage PDAC and chronic pancreatitis, suggesting a potential role of statins in chemo-preventive or early carcinogenesis settings [60]. Despite the controversial aspectes around the epidemiological association between statins and PDAC [61–64], there is a strong biological rational indicating that lowering the blood lipid-level may increase survival [65].

Taken together, cholesterol homeostasis regulation through restoration of NR5A2 function or statins administration may become a field of future investigation for elderly PDAC patients, aiming to identify co-adjuvants and chronic modulators of chemotherapy characterized by low toxicity [66].

Conclusions

The global population aging is a crucial element that at least in part explains the increased incidence of pancreatic cancer over the last years. In the near future the management of elderly patients affected by PDAC will gain crucial relevance and it will become a major public health issue.

We reviewed here a number of studies showing that aging itself does not preclude the use of chemotherapy, since older patients seem to benefit from anticancer treatments similarly to the younger ones, even if reduced-doses chemotherapy and improved support therapy are often necessary to preserve tolerability. Since available evidence is mainly derived from retrospective small series of cases, unplanned subset analyses and case-reports, the data are inadequate to provide robust, evidence-based recommendations for this setting of patients. Moreover, the interpretation may be biased by the heterogeneity of the elderly population itself, since the cutoff of 65 years proposed by WHO has intrinsic limitations and it is often inadequate to estimate the individual residual life expectancy and functional reserve. In addition, none of the reviewed studies provided data on patients' quality of life (QoL) during treatment. Since function preservation and QoL maintenance are major goals of geriatric oncology, implementing the evaluation of such parameters might determine the choice among alternative forms of life-prolongation and palliative treatments over active anticancer therapy.

Altogether, the lack of elderly-dedicated randomized trials, together with the heterogeneous definition of elderly across studies, makes it challenging to draw guidelines for the management of old cancer patients.

Accordingly, age-focused clinical trials, aiming to assess the age-related risk-benefit ratio and potential prognostic markers able to select patients who may benefit more from chemotherapy are eagerly needed. From the clinical perspective, a multidisciplinary geriatric oncology team and a palliative care-early access are crucial elements that need to be implemented and better integrated in daily practice. Not least, improving the identification of molecular markers able to individualize treatments, predict survival and forecast toxicity should be a primary aim of molecular medicine in the next years.

Conflicts of interest

All other authors declare no competing interests.

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