

HIGHLIGHT ARTICLE

Elderly Patients with Pancreatic Cancer

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ABSTRACT

Pancreatic cancer marked significant increase of incidence during the last decades in the elderly population. Despite the certain increase of incidence there are no international guidelines for elderly patients who are suffering from pancreatic cancer. During the ASCO Annual Meeting 2014, two abstracts focusing on elderly patients suffering from different histological types of pancreatic cancer were presented. The first retrospective study (Abstract # 4119) showed the benefit of the systemic treatment on overall survival for elderly patients with stage IV pancreatic adenocarcinoma. The second retrospective study (Abstract # 4112) demonstrates the positive effect of somatostatin analogue (octreotide-LAR) treatment on overall survival for elderly patients with neuroendocrine pancreatic carcinoma.

What Did We Know Before ASCO 2014?

The incidence of cancer is increasing with age and the probability for elderly persons of suffering from cancer is 1:3. Therefore, cancer represents the first cause of death for this age subgroup [1]. In addition, pancreatic cancer represents 3% of all cancers and it is the 4th most common cause of cancer death at the age of 70 and above [1]. Finally, even if guidelines for treatment of elderly cancer patients do exist, there are no recommendations regarding the treatment of elderly patients with pancreatic cancer.

Age represents a major risk factor for developing cancer, but it does not represent a contra-indication for the administration of the standard of care treatment [2]. The International Society of Geriatric Oncology (SIOG) established a predictive comprehensive geriatric assessment scale (CGA) which identifies patients who may profit from antineoplastic therapy.

More than 75% of all pancreatic tumors are adenocarcinomas, which have to be treated according to multidisciplinary approaches. Pancreatico-duodenectomy (Whipple procedure) with tumor resection and high rates of negative margins (RO) remains the only curative

option with acceptable mortality rates (< 5%) [3]. The French surgical series regarding resection of pancreatic adenocarcinoma in elderly patients was presented during the geriatric oncology meeting 2011 in Paris. The mortality rates were less than 5% (3.7% for < 70y and 4.4% for > 70y). Despite these beneficial results, more than 80% of newly diagnosed patients with pancreatic cancer do not meet the existing resection criteria [4].

According to the NCCN guidelines adjuvant chemotherapy with gemcitabine or 5-FU plus leucovorin, which is associated with median survival rates of 20 to 23 months, represents category I of recommendation for patients with pancreatic cancer [5, 6]. The most important trials were the CONKO-001 and the ESPAC-3. These studies, which also included elderly patients, reported about low percentages of grade 3-4 adverse side effects (7.5%) and satisfactory survival rates for patients who were treated with gemcitabine monotherapy.

It seems that particular subgroups of patients with locally advanced non resectable, but non metastatic pancreatic cancer, profit from chemotherapy or chemo-irradiation. However, guidelines for these patients do not exist [7, 8]. The findings of the phase III study of Chauffert et al., which compared radio-chemotherapy with chemotherapy alone for patients with locally advanced non resectable pancreatic adenocarcinoma, showed that chemotherapy alone was more beneficial on survival outcomes and well tolerated than combined chemo-irradiation [9]. Due to severe toxicity reported in clinical trials concerning locally advanced non resectable pancreatic adenocarcinoma treated with combine radio-chemotherapy, the choice of chemotherapy alone seems more appropriate for the elderly patients of the same stage [7-9]. Systemic therapy is the gold standard treatment for metastatic adenocarcinoma of the pancreas.

Key words Aged; Neuroendocrine Tumors; Pancreatic Neoplasms; Somatostatin

Abbreviations SEER: Surveillance, Epidemiology and End Results

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Conroy et al., compared the gold standard gemcitabine mono therapy with the combination of FOLFIRINOX and demonstrate that the combination FOLFIRINOX is superior to gemcitabine monotherapy since median overall survival and progression free survival was 11.1 vs. 6.8 and 6.4 vs. 3.3 respectively [10]. The patients included into this study were at the age of 75 years and less. Therefore, the presented results are not representative for elderly patients. Another study demonstrated that gemcitabine monotherapy is well tolerated and associated with acceptable overall survival rates even if administered to elderly patients [11]. Therefore, this treatment remains the gold standard for these patients [11] (Table 1).

Pancreatic adenocarcinomas represent the majority of pancreatic cancers, but a variety of different histological subtypes do exist. Although pancreatic neuroendocrine tumors originate in pancreas are classified as a subgroup of the neuroendocrine tumors (NETs). All NETs derived by the diffuse endocrine system cells, therefore, patients with advanced or metastatic NETs often develop secondary hormonal syndromes because of hormonal hypersecretion. A recent epidemiological study reports about a significant increase regarding the incidence of NETs showing that these tumors are the second most common tumors of the gastrointestinal system [12]. The same study confirmed the results of previous studies which showed increased incidence of NETs in the older population (25% over the age 75y). According to the NCCN guidelines the treatment options for these tumors include surgery, biotherapy, chemotherapy, radiotherapy and targeted therapies. In addition a watch and wait strategy might be useful for non-progressing tumors. The choice of the appropriate treatment modality depends on clinical stage, presence of clinical symptoms and the rate of tumor growth. Somatostatin analogues are used to control hormonal symptoms which are presented mainly in metastatic patients [13]. Rinke et al. presented the results

of the randomized PROMID trial. This study compared octreotide-LAR (OCT-L) vs. placebo for patients with stage IV NETs and showed a significant benefit regarding tumor progression for the OCT-L arm (14.3 vs. 6 months) [14]. The recent CLARINET study was conducted for patients with locally advanced or metastatic NETs who received somatostatin analogues (lanreotide) or placebo. This study demonstrates significant benefit for the treatment with somatostatin analogues (progression free survival >24 vs. 18 months) [15].

What Did We Learn at ASCO 2014?

Treatment, Outcomes, and Clinical Trial Participation in Very Elderly Patients (Pts) with Metastatic Pancreas Cancer

Li et al. presented the results of a retrospective study about elderly patients with metastatic pancreatic cancer who were referred to the Memorial Sloan Kettering Cancer Centre between 2005 and 2013 [16]. The age of patients who participated this study was >75y. Three subgroups were defined according to age (subgroup I: 75-79 years, subgroup II: 80-84 years and subgroup III: > 85 years). The data that were recorded were demographical, clinical (performance status, laboratory results and comorbidities), tumor related (primary site, site of metastases, number of metastases), treatment related (type of treatment, therapeutic agents), outcome related (overall survival) and finally related to the admission to a clinical trial (participation and type of clinical trial). In total 237 patients were included into the study, but only 83% of patients received the standard of care treatment and significant difference in overall survival noted. Overall survival was 7.1m for subgroup I, 7.3m for subgroup II and 5.9m for subgroup III. Only 5% of the patients participated in a clinical trial. In conclusion, there is a gain in overall survival in defined group of elderly patients with metastatic pancreatic cancer from the chemotherapy (Table 2).

Table 1. Treatment recommendation for elderly patients with pancreatic adenocarcinoma according to stage.

| Stage of Pancreatic Cancer | Treatment Recommendation for Elderly Patients with Pancreatic Cancer |
|--------------------------------------|--|
| Resectable Stage | Pancreatico-duodenectomy +/- adjuvant gemcitabine |
| Locally Advanced/ Unresectable Stage | Gemcitabine monotherapy |
| Advanced/Metastatic | Gemcitabine monotherapy |

Table 2. Results of elderly patients with stage IV pancreatic adenocarcinoma (Li D, et al.; Abstract # 4119 [16]).

| Age(y) | 75-79 | 80-84 | 85+ |
|--------------------------------------|-----------|----------|----------|
| N | 114 | 84 | 39 |
| Male | 51 | 40 | 13 |
| Female | 63 | 44 | 26 |
| ECOG PS | | | |
| 0-1 | 69 | 51 | 24 |
| 2 | 37 | 24 | 10 |
| 3+ | 8 | 9 | 5 |
| Charlson Comorbid Index (Median) | 5 | 5 | 6 |
| Chemotherapy Use | 101 (89%) | 70 (83%) | 25 (64%) |
| Clinical Trial Participation | 43 (38%) | 29 (34%) | 5 (13%) |
| Participation in a Therapeutic Trial | 9 (8%) | 4 (5%) | - |
| OS (Median Months) | | | |
| Systemic Therapy | 7.1 | 7.3 | 5.9 |
| No Therapy | | | |

Octreotide LAR (OCT-L) Among Elderly Patients with Stage IV Neuroendocrine Tumors (NETs)

Based on the beneficial results of somatostatin analogues treatment for patients with NETs on progression free survival shown by two randomized phase III trials (PROMID and CLARINET), Shen et al. studied retrospectively the effect of OCT-L on overall survival for these patients [17]. The study population consisted of patients from the SEER-database with stage IV NETs who were treated between 1999 and 2009. Exclusion criteria were age under 65 years, high risk histological characteristics (poorly differentiated, grade 3), participation in HMOs and inadequate follow up. The data that were recorded and analyzed were demographical (age, gender, race, socio-economic status, lifestyle, geographic area), treatment involved (surgery, liver surgery, chemotherapy, radiotherapy), primary site involvement (TNM, grade, time of diagnosis, comorbidities). 1176 patients were identified and included into the study. Out of these patients, only 233 (19.8%) patients received OCT-L within the first 12 months from diagnosis. Approximately, 76% and 24% of the OCT-L and the non OCT-L patients had a carcinoid syndrome, respectively. The addition of OCT-L resulted in an absolute benefit of 11 months for median survival. The benefit on overall survival was significant for all patients who received OCT-L irrespective of having a carcinoid syndrome. Finally, the authors concluded that elderly patients with stage IV NETs profit from OCT-L treatment, regardless the presence of carcinoid syndrome. However, additional studies are needed to confirm these results.

Discussion

The absence of international guidelines for the management of elderly patients with pancreatic cancer has to be ascribed to the limited number of available clinical trials. The treatment recommendation of SIOG is based on the existing clinical trials for which were performed for adult patients in general. Elderly patients with operable pancreatic adenocarcinoma are mostly considered as candidates for pancreatoduodenectomy, which is associated with acceptable mortality rates [3]. If adjuvant systemic therapy is administered to these patients, gemcitabine monotherapy is considered as the treatment of choice [5, 6]. Elderly patients with locally advanced or unresectable pancreatic adenocarcinoma should be treated with gemcitabine monotherapy as well, since concurrent chemo-irradiation, which represents an alternate option, is less tolerable [9]. For all patients

with metastatic pancreatic adenocarcinoma the treatment of choice is FOLFIRINOX, due to improved rates of progression free survival and overall survival compared to gemcitabine monotherapy [10]. According to the NCCN guidelines gemcitabine monotherapy is the recommended treatment for patients with metastatic pancreatic cancer and poor performance status irrespective of age. However, the increased rates of serious adverse effects which are associated with FOLFIRINOX make it unsuitable for elderly patients. Therefore, SIOG suggests gemcitabine monotherapy for elderly patients with metastatic pancreatic cancer [11].

During the ASCO Annual Meeting 2014, Li et al. presented a study with patients over the age of 80 years with stage IV pancreatic adenocarcinoma [16]. The authors concluded that elderly patients profit from the standard treatment regimen. The main limitations of this study are that it was retrospective and monocentric. In addition, information about the chemotherapeutic agents, toxicity and tolerance is lacking for the 83% of the total study population who received systemic therapy. Finally, the minority of the patients who participated the study received treatment based on prospective protocols (8% subgroup I, 5% subgroup II, 0% subgroup III). These results have therefore, to be confirmed by future randomized phase III trials.

The beneficial effect of somatostatin analogue for patients who are suffering from locally advanced or metastatic NETs was shown by two randomized phase III studies (PROMID and CLARINET) (14.15). Both studies showed significantly improved progression free survival rates for the patients who received somatostatin analogue. Based on these two studies the NCCN recommend somatostatin analogues for the control of secondary symptoms. During the ASCO Annual Meeting 2014, Chen et al. presented retrospective data about survival outcomes of elderly patients with stage IV NETs who were treated with OCT-L or did not receive any treatment. Treatment with OCT-L was related to significantly improved overall survival rates, regardless of the presence of secondary syndromes. However, the number of patients who received OCT-L was rather low compared to the total number of study patients.

In conclusion, additional future randomized phase III trials are needed to establish guidelines for the management of elderly patients with pancreatic cancer. Therefore, encouragement by the treating physicians, of elderly patients to participate clinical trials, will play a pivotal role to achieve this aim Table 3.

Table 3. Take home points after ASCO 2014.

| Take home points | Before ASCO 2014 | After ASCO 2014 |
|---|---|--|
| Elderly patients with stage IV pancreatic adenocarcinoma | Consider 1st line treatment with gemcitabine due to same efficacy and safety compared to adults | Standard treatment marks benefit in overall survival |
| Elderly patients with stage IV NETs | Somatostatin analogue Control of secondary syndromes Benefit on progression free survival | Somatostatin analogue Benefit overall survival |

Conflict of Interest

The authors have no potential conflict of interest.

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