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EDITORIAL

Any progress in pancreatic cancer?

Almost six years ago I wrote an editorial in this journal starting with the same words as constitute the title of this editorial [1]. It was written to an article by Simianu et al. [2], where the authors concluded that ''the modern area has witnessed great progress, with gradually evolving attitudes towards the surgical intervention. . .''. My own response to the question mark was summarized in the following word ''well''. In the text, I concluded that ''progress in pancreatic cancer has been seen, but it has been extremely slow and still only incremental''. Has any progress then been seen during the past 5–6 years?

The purpose of this editorial is not to give a comprehensive update of progress but rather to give editorial perspectives on six articles about pancreatic cancer published in this issue together with some perspectives on the progress.

Zijlstra et al. investigated whether long-term survival exists in pancreatic adenocarcinoma in a population-based study from the Netherlands [3]. The study, including 2564 patients of whom 1365 had a morphologically verified pancreatic adenocarcinoma, covers the period from 1993 to 2008 and is thus not of immediate interest for the question of whether recent progress has influenced population statistics. Reporting of population statistics are normally delayed for quite some time; the most recent update from EUROCARE also only covers the period until 2007 [4]. The authors conclude that long-term survival among patients with pancreatic adenocarcinoma is extremely rare, whether morphologically verified or unverified (1.7% vs. 1.3%). Most of the patients with long-term survival without morphological verification did not have a pancreatic adenocarcinoma. Twenty-one of the 24 long-term survivors in the verified cohort had undergone surgical resection; five-year survival after resection was 10.1%, a figure in line with what previously has been reported multiple times in patients usually not given adjuvant chemotherapy. Of note was that half of the surgically resected five-year survivors eventually died of recurrent disease, further emphasizing the conclusion that long-term survival and cure is extremely rare, although existing. This study sets the scene of the well known extremely poor survival of pancreatic cancer patients, also reported from many other countries with no improvement up until about 2009 [5–8]. In an update of Danish data [9], one-year survival has improved from 2007 to 2012 in patients younger than 80 years, whereas no improvement was seen in five-year survival except slightly for females less than 70 years. Population statistics are, however, hampered by both under- and over-reporting of pancreatic cancers [5,10,11].

In yet another Dutch population-based study, reported in Acta Oncologica last year [12], it was not possible to detect any improvement in median or 1–2-year survival in metastatic pancreatic cancers from the early 1990s to 2009–2010. In spite of an increase in the use of palliative chemotherapy from 10% to 27%, median survival remained at 10 weeks. Treated patients had longer survival than non-treated (25 weeks, i.e. less than six months vs. eight weeks), partly because the treatment prolongs life but to an even greater extent caused by selection. During the almost 20-year time period, the proportion of the 1494 patients who had metastatic disease increased from 35% to 59%, likely being a result of better diagnostics tools. This stage migration should result in longer survival since less metastatic tumor burden could be discovered, but apparently this was not the case. The two most recent developments in palliative chemotherapy in pancreatic cancer, FOLFIRINOX [13] and nab-paclitaxel with gemcitabine [14] were not used. If the study had been repeated let us say between 2013 and 2014 when these treatments were available, survival of actively treated patients would be longer and likely well above six months, but I question whether median survival of all patients would be much longer than the 2½ months seen during the preceding 20 years. Trial patients are selected and not representative of the background population.

The first part of the title of the above mentioned Dutch study [12], ''Ten weeks to live:'' illustrates the dilemma of administrating potentially toxic chemotherapy during the end of life (EOL), often the last 30 days. In a Norwegian study, also recently published in Acta Oncologica [15], pancreatic cancer was the solid tumor where the highest proportion (31%) received chemotherapy during the last 30 days of life, with lung cancer being second, 19%. In colorectal cancer, only 6% received this. Intuitively, many consider these proportions treated that close to death too high, as the benefit is minimal and toxicity definite. However, with the rapid clinical course of a pancreatic cancer in many patients and treatments that have proven effects on survival and well being, albeit benefitting less than half of the patients, many patients will receive therapy during their EOL. Hopefully, the initiation of treatment has been preceded by thorough discussions with the patients and their relatives about the clear risk of no benefit and only harm. If treatment is not initiated, the chance to have a longer life, with improved possibilities to prepare for the ultimate death, will be entirely absent. Using gemcitabine alone, you could argue whether the possibilities for a gain were sufficiently large, although the toxicity to gemcitabine is often minor. The addition of either capecitabine [16,17] or nab-paclitaxel [14,18] to gemcitabine also results in small or almost incremental gains, questioning their use. However, the combinations result in the sum of two incremental gains, being superior to what best supportive care can result in, and no longer incremental, motivating their use in good performance patients in spite of increased toxicity.

The efficacy of adding postoperative chemotherapy after pancreatic cancer surgery was shown already during the first decade of this century [19,20]. Since then, adjuvant chemotherapy using either a fluoropyrimidine or gemcitabine has been standard therapy at most sites after a surgical R0/R1 resection, with an expected doubling of long-term survival [21,22]. Norwegian researchers [23] retrospectively evaluated 203 patients curatively resected and planned for adjuvant chemotherapy. Of those, 77 (38%) patients never initiated this therapy, mainly because of early disease progression or postoperative complications. Of the remaining patients about 2/3 did not complete the adjuvant therapy and overall, only 85 (42%) of those initially planned to receive adjuvant therapy completed it. For obvious reasons patients who completed the adjuvant therapy did much better than those who did not or did not initiate it. The results likely reflect common routines in non-selected patients and may indicate that even if adjuvant chemotherapy has proven to be efficacious in randomized studies, the impact on overall survival in populations will be limited. More efficacious therapy, as presently reported in metastatic pancreatic cancer may have greater impact also in the adjuvant situation and is presently explored. These treatments [13,14,16,17] will not influence survival of those who progress early or have complications to surgery and completion rates may be less due to increased toxicity.

The outcome of pancreatic cancer surgery in elderly patients has been explored by van der Geest et al. [24]. Of 3845 patients, from a study base of 20 005 patients with primary pancreatic or periampullary cancer, who underwent tumor resection, postoperative mortality after 30 and 90 days increased with increasing age, particularly if the patient was over 80 years old. After 30 days, it was 4% for those under 70 years and 8% for those above 80 years. The corresponding numbers after 90 days were 6% and 12%, respectively. However, for those elderly patients who survived 90 days, overall survival was close to that of younger patients. As reported for virtually all cancer sites and treatments, old age should not per se exclude patients from an intervention that may prolong life or ultimately cure them. Mortality and complications are increased, but with proper patient selection, they are often reasonable.

As in other tumor types, neo-adjuvant or induction chemotherapy and chemoradiotherapy may have greater possibilities to favorably influence long-term survival than adjuvant chemotherapy/chemoradiotherapy has. Early attempts, particularly in those considered borderline resectable but also in locally advanced non-metastatic pancreatic adenocarcinomas have been favorable, particularly when the triple combination FOLFIRINOX has been used [25–27]. However, these data must so far be interpreted with great care, and patient selection to these intensive treatment schedules may well explain the apparently favorable results. It is, however, my belief that recent improvements in radiation delivery should be explored to a greater extent, in locally advanced pancreatic cancer to improve outcome [28–31].

In a subgroup analysis of a randomized German trial comparing first-line treatment with either capecitabine plus erlotinib or gemcitabine plus erlotinib [32], it was found that patients who developed hand-foot syndrome within the first three cycles had better time to treatment failure and overall survival than those who did not. The study included rather few individuals in the capecitabine plus erlotinib arm, but the difference remained also when only the subgroup of 70 patients who were on treatment with capecitabine for at least three cycles were analyzed. Thus, the guarantee-time bias was considered.

The response to palliative chemotherapy in biliary tract carcinoma is considered to be slightly better than that in pancreatic adenocarcinoma, although such inter-diagnoses comparisons are notoriously difficult. In an attempt to improve treatment results, cetuximab was added to a triple combination of gemcitabine, capecitabine and oxaliplatin, however, it failed to improve treatment results and should not be recommended for use even if it was considered to be well tolerated [33,34]. In pancreatic cancer, cetuximab likewise failed to add efficacy to gemcitabine in a large randomized study [35].

In order to improve response to chemotherapy, biomarkers have been extensively studied. One of the most studied biomarkers in pancreatic cancer has been human equilibrative nucleoside transporter 1 (hENT1) that together with the activating enzyme deoxycytidine kinase (dCK) have been linked to treatment response to gemcitabine. These two markers were explored in a study including 175 patients with resected periampullar cancers, including pancreatic adenocarcinomas, also reported in this issue [36]. hENT1 expression was an independent predictor of favorable outcome in the intestinal type periampullar cancers, but not in pancreatobiliary cancers. The authors argue that morphological subtype should be considered in future biomarker studies [36]. The study adds to the difficulties in finding clinically relevant biomarkers for response and outcome in pancreatic cancer.

In a retrospective study from MD Anderson, Houston, Texas, 199 patients with locally advanced pancreatic cancer treated with chemoradiotherapy between 2006 and 2012 were identified. Pretreatment thrombocytosis independently predicted inferior overall survival and progression-free survival, thus being yet another routinely collected parameter of potential clinical relevance for evaluating outcome [37].

The far majority of pancreatic cancers diagnosed worldwide are sporadic, however, 5–10% may be associated with inherited factors. Sharma et al. present four cases illustrating the association with mutations in BRCA1 or BRCA2 [38]. Though we are far from screening carriers of these mutations for pancreatic cancer, these mutations may have clinical impact of therapeutic relevance. BRCA mutation carriers have a potential for individualized treatments including targeted therapies, with better outcomes, irrespective of tumor type. One of the cases presented had a pathological complete response to FOLFIRINOX. Such excellent responses have been exceedingly rarely reported in pancreatic cancer.

Has progress then been made?

Groundbreaking policy changing treatments or other signs of significant progress will likely not primarily be published in Acta Oncologica, although the six articles published in this issue and additional articles recently published or to be

published later in the journal, and discussed above, contribute to improved knowledge of potential relevance for the treatment of patients with pancreas cancer. The prospective clinical trials with their strict patient inclusion criteria are fundamental for progress. Outcome research based upon studies done in well defined and large populations, to which several of the studies discussed belong, are likewise of great importance to better understand the clinical value of different treatments. Surgery can presently be safely performed in many patients, including the elderly if appropriately selected. However, cure after surgery is frequently not possible and the far majority of patients will recur. Adjuvant chemotherapy with treatments presently not considered most optimal in metastatic pancreatic cancer definitely reduces the risk of recurrence, but the absolute benefit is still small. The use of combinations of chemotherapy, particularly when given prior to surgery may yield better results, but remains to be tested and the increased toxicity may not always translate to better outcome. The incorporation of a taxane to gemcitabine as well as the triple combination of gemcitabine, 5-fluorouracil and oxaliplatin have improved the likelihood for metastatic cancer patients to respond to therapy and thus achieve symptomatic improvements, however, at the expense of increased toxicity. Quality of life outcomes have not been properly explored. In a study, the addition of nab-paclitaxel resulted in a median Q-TWiST gain of 1.0 month (95% confidence limits 0.1–1.9), considered by the authors to be clinically important [39].

Presently, much hope is put on immune therapies and particularly on the use of immune checkpoints inhibitors like pembrolizumab [40,41]. In a search on Clinicaltrials.gov, four such studies were found, but none of them included only pancreatic cancers. In a double-blind randomized phase II study, the Janus kinase (JAK) signal transducer and activator of transcription pathway ruxolitinib together with capecitabine in 127 patients having failed gemcitabine tended to improve both progression-free and overall survival (hazard ratios about 0.75–0.80). In the subgroup of patients with inflammation defined by CRP levels above median (13 mg/l), the overall survival difference was statistically significant (HR 0.47, 95% CI 0.26–0.85, median 2.7 vs. 1.8 months) [42].

In conclusion, progress has been made during the past 5–6 years, but similar to how I ended my editorial six years ago [1], it has been slow and the gains are still mostly incremental despite the substantially improved knowledge about basic tumor biology in pancreatic cancer. The improvements seen so far will likely not yet have any major impact on the dismal long-term prognosis in pancreatic cancer patients in a general population.

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