A multidisciplinary approach to improve treatment strategies for patients with hepatic or pancreatic cancer

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PART III

General discussion

[Failure is a much more faithful teacher than immediate success.
David DuChemin, world & humanitarian photographer]

CHAPTER 9

General discussion and Future perspectives

Summary

General Discussion and Future Perspectives

Part I–Hepatic perfusion for the treatment of unresectable liver metastases

In a recent report of the Dutch Melanoma Treatment Registry (DMTR) on metastasized uveal melanoma patients, who received all kinds of treatments, one-year survival is reported to be 47.8%. The authors state that the best results in terms of survival are among patients in whom surgery or locoregional procedures can be performed and among patients with solitary hepatic metastases. [1] Currently, no systemic therapy has shown to improve survival for patients with metastatic uveal melanoma (UM) and there is no specific standard of care. Therefore patients should be treated in clinical trials. [1] This underlines the urge for development of successful (locoregional) therapy, like described in this thesis. The results of percutaneous hepatic perfusion (PHP) are promising as described in Chapter 6; one-year overall survival was 80%. Median overall survival was 29 months. PHP is amongst the few treatment options for UM that seems to really increase survival time and holds promise for further investigations.

Combination of systemic and locoregional therapy

Research on systemic therapy agents for UM is ongoing. Several authors suggest that combined treatment could be considered as part of a multimodal treatment approach combined with locoregional interventions. [2-4] A significant part of the patients treated with PHP, developed extrahepatic disease in the follow-up, whereas the liver metastases were mainly stable. Effective systemic treatments for extrahepatic metastases are urgently needed to further improve survival.

Targeted therapy

Uveal melanoma differs significantly from cutaneous melanoma at biological level. Unlike cutaneous melanoma (characterized by BRAF or NRAS mutations), mutations in GNAQ or GNA11 are present in about 80% of primary uveal melanomas. Consequently, advances in targeted therapy for cutaneous melanoma are not applicable to metastatic uveal melanoma; treatment with BRAF inhibitors (such as vemurafenib or dabrafenib) are not effective. [5-7] MEK-inhibitors (like selumetinib) achieved tumour regression, but the effects were not clinically relevant.[8, 9] A phase II study (2014) comparing selumitinib (a MEK inhibitor) to chemotherapy (temozolomide or dacarbazine) led to a median overall survival of 11.8 months in the

selumitinib group (versus 9.1) and a median progression-free survival of 16 weeks (versus 7 weeks). [9] The randomized placebo-controlled SUMIT trial, investigated adding a MEK-inhibitor (selumetinib) to chemotherapy in metastatic UM patients without an effect on progression free survival (2.8 versus 1.8 months).[10, 11] Other targeted therapy trials (such as AEB071) were preliminary closed due to toxicity.

Checkpoint inhibitors

Checkpoint inhibition, also called immunotherapy, was investigated as treatment for UM after ipilimumab (anti-CTLA-4), pembrolizumab (anti-PD-1) and nivolumab (anti-PD-1) had shown strong survival benefits for cutaneous melanoma patients. [12-14] Limited clinical activity was reported in several phase I/II trials investigating monotherapy in UM patients; overall survival data of 3-7 months were reported. [2-4, 15-17] The limited efficacy of checkpoint inhibitors in uveal melanoma has led to the agreement among members of the 'Dutch Working Group on immunotherapy and oncology' (WIN-O) not to treat patients with immune checkpoint inhibitors outside a clinical trial. [1] Currently, a phase II randomized multicenter study is recruiting patients with metastasized UM investigating the safety and efficacy of a specific antibody acting on T-cells (IMCgp100) compared to either dacarbazine, ipilimumab or pembrolizumab. An interim analysis of 19 patients showed a prolonged response to treatment and longer survival times. (EudraCT 2016-002236-32)

Dendritic cell therapy

Pre-clinical work on the combination of radiofrequency ablation (RFA) and a checkpoint inhibitor showed enhanced antigen-loading of natural present dendritic cells (DCs), and induced long-lasting anti-tumour immune responses in a murine melanoma model. Dendritic cells are antigen-presenting cells that can activate antigen-specific T-cells with anti-tumour immune activity. This principle was used in the development of dendritic cells loaded with tumour-antigens based on the patient's primary tumour genetics, as adjuvant treatment for patients with stage-IV melanoma after resection. Transient flu-like symptoms were reported as adverse effects. Currently, randomized phase III trials are recruiting to determine whether dendritic cell vaccination can prevent or delay progression of disease for uveal melanoma patients. (NCT01983748). [18] To further investigate this combination a phase I/II study was conducted to investigate the safety and efficacy of the combination of RFA and ipilimumab in UM patients with liver metastases. In one evaluable patient, a significant broadening of the melanoma-associated antigens T cells was observed. Also clinical and biological activity was observed. [19]

In future trials, combinations of locoregional and (yet to be defined) systemic therapy could be investigated. During PHP tumour cells are damaged by the alkylating

agent melphalan. Concurrent administration of currently investigated systemic therapy could be investigated, to determine whether this enhances anti-tumour efficacy. The combination of ipilimumab and nivolumab has achieved improved response rates in several clinical studies. [20] [21]. Interestingly, the majority of responders underwent liver-directed therapy (TACE, surgery or PHP) prior to systemic therapy. In the current CHOPIN trial a combination therapy with immunotherapy (ipilimumab with nivolumab) and PHP with chemotherapy (melphalan) is assessed for the treatment of disseminated uveal melanoma. (NCT04283890).

Besides combinations of therapies, different ways of administration are being studied. Recently, a randomized controlled trial was initiated investigating adjuvant hepatic arterial infusion pump (HAIP) chemotherapy for patients with resectabel colorectal liver metastases. In this PUMP trial (NTR7493) intra-arterial floxuridine is delivered in the hepatic artery via a surgically implanted pump with a catheter in the gastroduodenal artery. Like PHP, the biological rationale for HAIP is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumours. This HAIP technique has been previously investigated for unresectable cholangiocarcinoma (combined with systemic therapy) and appeared to be active and tolerable [22]. It has not been investigated for uveal melanoma liver metastases.

In the meanwhile, genetic investigations are ongoing. It is known that gene expression profiling is very accurate in predicting metastatic risk, more than clinical stage [23]. Monosomy 3 is a common chromosomal abnormality in uveal melanoma and is associated with metastatic disease. Simultaneous monosomy 3 and chromosome 8 alterations, are associated with a worse prognosis. [15] The previously mentioned mutations in GNAQ or GNA11 (which upregulate hepatocyte growth factor) led to the development of specific inhibitors (currently being investigated preclinical trials). [24, 25]This profiling could be used for patient-tailored treatment selection; if the genetic profile predicts that the patient will not benefit from the treatment, the adverse events can also be prevented. [15] This will help clinicians to select the best treatment option for patients with uveal melanoma, maybe even in a very early stage.

Part II–Tailored care for patients with pancreatic cancer

The importance of auditing and data registries

A significant number (>34%) of pancreatic cancer (PC) patients is over the age of 70 years at diagnosis. [26] In clinical trials, elderly patients are often not included, consequently the efficacy of (chemo-)therapy in older patients remains unclear. There are only few studies evaluating the efficacy and safety of chemotherapeutic

treatment for older PC patients. [27] Audits and registry structures cover the entire population, including elderly patients. Therefore, auditing cancer care with adequate case-mix adjustments is a very effective instrument to gain insight in care patterns, determine best practices and have a possible impact on outcome, also for specific groups such as elderly patients. Latter form the basis of the foundation of Eurecca (European REgistration of Cancer Care). Following the roadmap of previous projects on colorectal, breast and upper gastrointestinal cancer, Eurecca Pancreas was initiated (Chapter 7). In 2018, the results of a first comparison of data from the Eurecca Pancreas Consortium were reported providing an insight in clinical practices in several countries in Europa as well as regional registries. Variations in treatment and outcomes of patients who underwent tumour resection for stage I and II pancreatic adenocarcinoma illustrate the difference in implementation of universally accepted guidelines. It also provides a basis for further investigation of the best practices and indicates the need of uniform registration in order to perform international comparisons. [28] This will hopefully lead to a population-based audit structure that covers all pancreatic cancer patients across the participating countries (and eventually across Europe). The aim is to eventually monitor the quality of care of European pancreatic cancer patients, as well as perform analysis on patient groups that deviate from guidelines such as the elderly. These data should be studied with great care, considering that differences in survival and other outcomes are not only based on treatment strategies, but differ between countries, regions and centres based on other factors. Lifestyle factors, but also stage of disease at time of presentation and genetics (e.g. ethnicity and ABO blood group). [27] [28]

Adjust treatment to age

Following determination of best practices in the treatment of elderly pancreatic cancer patients, they have to be implemented in clinical practice. A collaborative geriatric and oncology management can optimize care in elderly patients. [29] It leads to greater attention being paid to existing comorbidity and geriatric issues, which may result in better selection of adequate treatment (or no treatment), prevention of complications, and lower the risk of patient deconditioning. Integrated geriatric care for (the recognition of frail) elderly has proven to increase efficiency of healthcare, leading to retaining independence and an optimal quality of life. [30] [31] At Moffit Cancer Center, Tampa (Florida, US) specialized care tailored to geriatric cancer patients is offered. A comparison was made between collected patient data from Moffit and the Dutch Cancer Registry, as described in this thesis (Chapter 8). Whereas survival seems to improve with palliative systemic treatment, this benefit might be counterbalanced by toxicity and quality of life concerns; an important consideration for elderly patients. Unfortunately, no quality of data was available for these cohorts. For young patients, prolongation of life might be the most important end point;

however, elderly patients may prefer quality of life (their cognitive function, their social situation/capability to stay at home) above quantity of life. There is a need for delineation of relevant clinical endpoints for older individuals, which can then be uniformly incorporated into future clinical trials. [32]

For patients presenting with resectable pancreatic cancer, it is important to question the patient's condition and whether the patient will benefit from the treatment, taking life expectancy into account. Surgical resection with or without systemic therapy is associated with a high risk of perioperative morbidity and mortality, especially in older patients. [26] Apparently contradictory conclusions are reported concerning surgical treatment of elderly patients with pancreatic cancer; patients over 65 years of age would suffer more from side effects and post-treatment morbidity, and mortality would be higher amongst patients older than 70 years. [33] [34] On the other hand it is stated that pancreatico-duodenectomy can be performed safely in carefully selected patients of 75 years and older and that age does not influence the postoperative outcome. [35] [36] A recent trial comparing time to functional recovery after minimal invasive- versus open distal pancreatectomy for left-sided pancreatic tumours favoured minimal invasive surgery and was associated with less delayed gastric emptying and better quality of life without increasing costs. [37] Age specific analysis of these data will have to indicate whether there is also a difference for elderly patients.

Decision aid tools

For breast cancer, research on elderly patients is ongoing. [38] Trials are especially designed and population-based studies are used to develop prediction models. [39]The Dutch Pancreatic Cancer Group (DPCG) developed several decision aid tools for physicians to help gain insight in survival after surgery of pancreatic cancer which may be useful for counselling patients during follow-up [Pancreascalculator, found on DPCG website]. Elderly patients however might benefit from decision aid tools incorporating quality of life, instead of only survival data. Decision aid tools indicating the benefit of a specific treatment, such as Predict for breast cancer patients, could be of help in clinical practice and shared-decision making with elderly pancreatic cancer patients. Recently, a 'consultation card' was developed for patients with pancreatic cancer, as an initiative of a patient federation (Living With Hope) and the Dutch Society of Surgery (NVVH). At this card information about different treatment options after surgery are displayed in a scheme. These valuable tools can be used as supportive measure in shared decision making. [consultkaart NL].

Systemic therapy for patients with pancreatic cancer

Neoadjuvant chemotherapy with gemcitabine in The Netherlands was only administered in a clinical trial setting: the national randomized controlled Preopanc-1 trial. Preliminary outcomes, as presented by Van Tienhoven et al. at the 2018 ASCO Annual Meeting show that neoadjuvant chemotherapy increases median overall survival (17.1 months after neo-adjuvant therapy, compared to 13.7 after immediate surgery). For patients with a successful surgical resection this difference was even greater; 42.1 versus 16.8 months. [40] In the phase III PRODIGE 24 study, Folfirinox (modified scheme) was compared to gemcitabin in fit patients with pancreatic ductal adenocarcinoma (18-79 years of age) after resection. Median overall survival (OS) was 54.4 months in the mFolirinox group compared with 35.0 months for standard gemcitabine. [41] Also for metastatic PC patients (age 25-76 years) folfirinox improved overall survival compared to gemcitabine (11.1 months versus 6.8 months). [42] In continuation of Preopanc-1, knowing the results of folfirinox schemes, Preopanc-2 (NTR7292) is an RCT currently investigating the (cost-) effectiveness of neoadjuvant folfirinox versus neoadjuvant gemcitabine, and adjuvant gemcitabine for (borderline) resectable pancreatic cancer. The results have to be awaited. In 2017 a retrospective analysis reported on survival data of fit patients over 70 years old with inoperable pancreatic cancer treated with folfirinox: median OS in elderly was similar to that reported in younger patients (ACCORD 11 trial (11.7 months vs 16.6 months, p=0.69)), although 57% of patients needed a dose reduction because of toxicity. [43] This indicates that elderly patients might benefit from treatment with an adjusted treatment scheme. Age specific analysis of recent clinical trial data could help to define recommendations in Dutch /European Guidelines for the treatment of elderly patients with pancreatic cancer.

The importance of medical care with a special focus on elderly patients, is also described in the Dutch Residents education Plan, called the CanBetter themes: one of the key items is care for elderly patients. [44] The new generation of medical specialists is trained in the treatment of this specific group of patients since there will be a growing number of elderly patients in need of (cancer) care.

In conclusion, population-based data, as well as specific trial data on subgroups of patients could be helpful in answering the question: what is the best available care for pancreatic cancer patients in a different stage of the disease or at a different age?