THE CONCEPT OF MAINTENANCE: MAY WE MOVE IT TO GASTRIC, PANCREATIC AND LIVER CANCERS?


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Abstract – The significant progresses recently achieved in the treatment of gastric, pancreatic and liver cancers have led clinicians to evaluate the opportunity to interrupt first-line treatments before disease progression and to consider maintenance therapies. In colorectal cancer, this strategy has produced remarkable advances, and patients whose disease is controlled after a few months of upfront therapy may derive clinical benefit and enjoy improved quality of life from continuing a less intensive treatment or early shifting to another, well-tolerated regimen. If the concept of maintenance may be applicable to other gastrointestinal malignancies is currently unknown, but the evidence is rapidly emerging.

KEYWORDS: Maintenance, Gastric cancer, Pancreatic cancer, Hepatocellular carcinoma.

INTRODUCTION

Maintenance chemotherapy, an important part of the treatment strategy of metastatic gastrointestinal tumours, is rapidly evolving. Over the past decade, three facts have contributed to extend median overall survival (OS) of gastrointestinal cancer patients with metastatic disease: a more profound understanding of the molecular biology of cancer, the development of new active drugs and the concept of a treatment strategy that includes pauses, re-challenges, and maintenance periods. In facts, the median OS for patients with metastatic colorectal cancer has surpassed 30 months in molecularly selected cases, and the median OS of patients with advanced gastric or pancreatic cancer has also significantly increased due to the introduction of novel regimens, second-line treatments, and target therapies. Despite the extension of median OS for patients diagnosed with gastric, pancreatic, or liver cancers, the vast majority of gastrointestinal tumours still remain incurable in their advanced phase and the goal of the overall therapeutic strategy focuses on disease control and maintenance of good quality of life (QoL).

In the meantime, the paradigm of continuing first-line therapy until disease progression or intolerable toxicity has been challenged. The introduction of more intense upfront regimens including cytotoxic drugs with potential cumulative toxicities as well as the survival improvements gained with the use of novel drugs have turned on the debate on the optimal upfront treatment duration. In particular, it is unclear if first-line treatment should be better continued until disease progression or rather discontinued after disease control has been achieved (usually after 4 to 6 months) to offer the patients some period of rest.
In this scenario, the example of colorectal cancer is paradigmatic. A more modern strategy to manage this disease include an induction phase with intensive chemotherapy followed by a maintenance window with a reduced dose of the same chemotherapy, changed non-cross-resistant drugs, or modified schedule of treatment\textsuperscript{8,9,13,14}. In fact, the aim of maintenance therapy is to extend (and reinforce) the favourable results achieved with first-line induction therapy; thus, maintenance therapy could only play a role after a successful first-line treatment (i.e. complete response, partial response or stable disease) has been completed\textsuperscript{15}. Moreover, the substantial toxicity profile of highly active drugs may be mitigated using maintenance, less intensive treatment, which may be associated with improved quality of life. In metastatic CRC, the continuation of first-line treatment beyond 4-6 months is supported by limited evidence\textsuperscript{16} and the role of maintenance strategy has been clearly established\textsuperscript{16}. The OPTIMOX-1 trial was the first large study suggesting that prolonging combination chemotherapy until disease progression is of limited clinical value\textsuperscript{17}. After these results, two other trials tested chemotherapy-free intervals during first-line therapy: the OPTIMOX-2 trial and the COIN trial. While the COIN trial demonstrated that intermittent chemotherapy with XELOX (capecitabine/leucovorin/oxaliplatin) or modified FOLFOX (5-fluorouracil/leucovorin/oxaliplatin) for 12 weeks followed by treatment interruption until disease progression and further 12 weeks of treatment was non-inferior in terms of OS to continuous combination chemotherapy until progression\textsuperscript{18}; the OPTIMOX-2 trial suggested that a complete interruption of chemotherapy may be detrimental\textsuperscript{19}. Antiangiogenic drugs have also been tested in the maintenance setting in a number of randomized clinical trials enrolling colorectal cancer patients with advanced disease\textsuperscript{20}

Although maintenance after first-line therapy has been studied in lung\textsuperscript{21,22}, breast\textsuperscript{23,24,25}, ovarian\textsuperscript{24,25} and colorectal cancer\textsuperscript{26,27}, its role remains uncertain in other gastrointestinal cancer. The aim of this review is to summarize experiences and evidence of use of maintenance therapy in non-colorectal metastatic gastrointestinal cancer, in particular in advanced gastric, pancreatic and hepatic cancers. There are two different strategies: A) switch maintenance, where patients are exposed to new non-cross-resistant cytotoxic drug or targeted agent that was not included in the previous induction treatment; and B) continuous maintenance, where a less-toxic part of the former regimen is used until disease progression.

### Maintenance in Advanced Gastric Cancer

Gastric cancer is one of the most common cancers worldwide, being the third most common cause of cancer-related death globally\textsuperscript{2}. In the US, approximately 22,220 patients are diagnosed annually, of whom 10,990 are expected to die because of disease progression\textsuperscript{1}. The majority of patients with gastric cancer were diagnosed with locally advanced or metastatic disease; thus, palliative chemotherapy represents the only therapeutic option, with the purpose of prolonging survival, relieving symptoms and improving QoL\textsuperscript{27-29}

Advanced gastric cancer (AGC) is a chemotherapy-sensitive disease, with various active drug from different therapy classes. Moreover, two new drugs have been approved for clinical use. Trastuzumab, a humanized monoclonal antibody that blocks HER2 activation, may be used in first-line in combination with chemotherapy; ramucirumab, a fully human immunoglobulin G1 monoclonal antibody targeting VEGFR-2, may be prescribed in pre-treated patients either alone or combined with single-agent paclitaxel\textsuperscript{12,13}

Although a large number of trials have been completed, multiple treatment options, with different intensity, may be selected as first-line treatment for advanced disease. Several drugs have shown good single-agent activity; however, the response rates range from 10% to 25% and the median duration of response is relatively short. Combination chemotherapy is associated with a statistically significant survival benefit compared with monotherapy in a meta-analysis of II phase II and III clinical trials with a total of 1,472 patients (P = 0.001)\textsuperscript{27}. Instead, the role of triplet regimens has been largely reconsidered because of potential toxicity and the unclear fitness with a long-term strategic treatment plan. The meta-analysis also showed that the combinations of 5-FU and cisplatin plus anthracycline have a significant survival benefit compared with the combinations of 5-FU and cisplatin (p < 0.0001)\textsuperscript{27}. However, even if the combination of a number of active drugs seems to be an intriguing possibility due to the demonstrated benefit in long-term outcome, this strategy also increases the toxicity rate and eventually leads to a reduction of treatment compliance\textsuperscript{26,31}. The prescription of a maintenance therapy after a more intensive upfront treatment could represent a good option to keep cancer under control and improve patients’ QoL.

To date, only the role of fluoropyrimidines as maintenance therapy has been explored in AGC\textsuperscript{22-24}. The efficacy and safety of capecitabine
as maintenance treatment after first-line chemotherapy in AGC has been evaluated in 287 Chinese patients who had previously received 6 cycles of oxaliplatin and capecitabine as first-line chemotherapy, without disease progression but with documented grade 2 or higher neuropathy. Overall, 222 patients interrupted the treatment and 64 patients received capecitabine as maintenance. The median PFS was 11.4 months [95% confidence interval (CI) 10.2-12.2 months] for patients who received maintenance therapy versus 7.1 months (95% CI 6.1-8.0 months) for those in the control group (p < 0.001). The multivariate analysis showed that the maintenance treatment was an independent prognostic factor. Moreover, the safety profile was consistently mild in the phase of maintenance treatment. Similar results emerged from a retrospective Turkish study that demonstrated a 9-month longer median PFS with a favourable safety profile for patients exposed to capecitabine as maintenance therapy.

In 2015, an Italian study group evaluated the efficacy and safety of FOLFOX-4 combination chemotherapy, followed by leucovorin/bolus and continuous infusion 5-fluorouracil as maintenance chemotherapy in patients older than 74 years diagnosed with AGC and with an impaired performance status. Overall, 38 patients with no evidence of disease progression after a maximum of 6 FOLFOX-4 cycles were enrolled in this study; they received maintenance treatment with LV/bolus and continuous infusion 5-FU every 2 weeks until disease progression or unacceptable toxicity. After completion of the oxaliplatin-based regimen, 47.3% patients achieved a partial response and 36.8% patients had stable disease. The 6-month disease-control rate was 47.3% (95% CI 30.9-64.1), the median PFS was 5.9 months (95% CI 4.7-6.8), and the median OS was 9.6 months (95% CI 8.1-11.7). The safety profile was acceptable, with grade 3 neutropenia occurred in 6 patients (15.7%), and grade 3 anaemia and thrombocytopenia occurred in 2 patients (5.2%).

Biologic drugs have also been evaluated as maintenance therapy for patients with AGC. In particular, the activity and safety of maintenance trastuzumab have been explored both in the pivotal randomized phase III trial and in a small retrospective analysis including HER2-positive AGC patients who received the HER2 inhibitor after a first-line doublet or triplet regimen. Therefore, patients who have been exposed to a first-line treatment lasting up to 6 months may be offered a simplified, less-intensive, maintenance treatment. This could be particularly intriguing when first-line combination chemotherapy included oxaliplatin, in order to reduce the risk of cumulative sensorial neuropathy. Although first-line treatment for AGC was continued until progression or toxicity within clinical trials, this paradigm is shifting towards the possibility of interrupting first-line treatment after 4 to 6 months of therapy, and the option of continuing with the only fluoropyrimidine could be reasonable, possibly associated with trastuzumab in patients treated for a HER2 positive disease.

Actually, the median upfront treatment duration of European patients with AGC seldom exceeds 6 months; consequently, often the treatment does not exceed this length. Thus, whether to stop or to mitigate the treatment before progression is not a frequent question in clinical practice. Generally, in this case, the decision whether to stop or continue treatment is clinical, based on a careful assessment of the risk/benefit analysis. All this always providing full information to the patient who needs to be involved in decision-making.

Other trials testing maintenance therapy in gastric cancer are ongoing. MANTRA is an Italian phase II randomized study that compares regorafenib to placebo in patients with no evidence of progressive disease after a first-line platinum and fluoropyrimidine-based chemotherapy for HER2-negative locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer. The primary endpoint is PFS, defined as the time from random assignment to progressive disease or death. Secondary endpoints are OS, safety, RR, and quality of life. After achieving disease control after platinum compounds and fluoropyrimidine-based regimes (up to 6 cycles of cisplatin and 5-fluorouracil or capecitabine, up to 12 cycles of FOLFOX, or up to 8 cycles of XELOX) patients will be randomly assigned to receive either placebo or regorafenib at the oral dose of 160 mg on days 1-21 every 4 weeks, until intolerance or disease progression. JAVELIN Gastric 100 is a phase III multicentric open-label trial that investigates maintenance therapy in a similar patients’ setting. After completing an induction phase encompassing a combination of oxaliplatin and a fluoropyrimidine for three months, patients are randomized to either a maintenance phase with avelumab at the dose of 10 mg/kg or to continuing the same chemotherapy doublet until disease progression, unacceptable toxicity, or consent withdrawal. The co-primary endpoints of the study are overall survival and progression-free survival.

ARMANI is a randomized, open-label, multicenter phase III trial that tests standard doses of ramucirumab plus paclitaxel as switch-maintenance therapy aiming at demonstrating a prolonged PFS in the experimental arm.
MAINTENANCE IN ADVANCED PANCREATIC CANCER

Pancreatic cancer is a leading cause of cancer-related death in Western Countries. Gemcitabine has been considered the treatment’s cornerstone of palliative chemotherapy in advanced pancreatic cancer (APC) for over 15 years, since gemcitabine-based combinations only minimally improved survival compared to gemcitabine alone. Recently, combination regimens such as FOLFIRINOX (5-FU/leucovorin/oxaliplatin/irinotecan), PEG (cisplatin/epirubicin/5-FU-gemcitabine), and gemcitabine-nabpaclitaxel have emerged as new effective options for patients with advanced disease. In the randomized PRODIGE 4/ACCORD 11 trial, median OS was longer for patients exposed to the triplet regimen compared to that reported for those treated with gemcitabine alone (median OS 11.1 vs. 6.8 months, p < 0.001). Also, a significant clinical benefit was achieved in the experimental arm (p < 0.001). However, the safety profile and the burden of related toxicities probably restrict the use of FOLFIRINOX to younger and fit patients. The combination of nabpaclitaxel and gemcitabine showed a significant survival gain over gemcitabine alone (8.7 months vs. 6.6 months, p < 0.001) and significantly improved the secondary endpoints with a better safety profile than FOLFIRINOX. Thus, over the last 3 years the median OS of APC has doubled from the 6 months of gemcitabine alone to the 9-11 months of combination therapy and this new setting of treatments, characterized by effective upfront chemotherapy regimen and the possibility of prolonged control of disease, could justify the approach of maintenance in pancreatic cancer. Reasonable options to be explored in this setting are represented by fluoropyrimidine monotherapy and targeted therapies. The effectiveness and tolerability of maintenance capcitabine administered to patients with advanced disease who had received the first-line FOLFIRINOX and without signs of progression after 4 cycles were studied in a retrospective analysis of 103 metastatic patients. In this study, 31 patients were initially treated with a minimum of four cycles of FOLFIRINOX and, if the disease was not progressed, they received capcitabine 2,000 mg/sqm day 1-14 q21; upon progression patients could be retreated with FOLFIRINOX. Median OS was 19 months with survival rates of 74% at 1 year and 24% at 2 years. Median PFS was 11 months, and after disease progression, FOLFIRINOX was administered to 14 patients owing a prolonged disease control.

Another therapeutic strategy to prolong disease control without impacting on quality of life is the use of a sequential, not cross-resistant scheme. FIRGEM, a phase II randomized trial, assigned 98 patients to first-line therapy alternating 4 cycles of a modified FOLFIRI regimen (FOLFIRI3) with 2 months of gemcitabine given as maintenance therapy versus gemcitabine alone until progression. The median OS was 3 months longer in the maintenance arm (11 months in the FIRGEM regimen vs. 8.2 months in the gemcitabine group). Overall, the FIRGEM strategy allows using oxaliplatin in second-line of treatment.

The role of 5-fluourouracil and leucovorin (5-FU/LV) as maintenance therapy will be explored in PANOPTIMOX trial that is still recruiting: patients are randomized to receive FOLFIRINOX regimen as reference regimen versus FOLFIRINOX regimen for 8 cycles with 5-FU/LV in maintenance versus FIRGEM regimen.

Angiogenic inhibitors have also been tested as maintenance therapy in patients with metastatic pancreatic cancer. Based on preclinical data showing its activity in murine models, sunitinib was compared to placebo in PACT-12. Patients without disease progression after 6 months of any gemcitabine-based first-line chemotherapy were randomly assigned to observation or sunitinib at the flat continuous dose of 37.5 mg daily. The trial met its primary endpoint showing a PFS rate at 6 months of 22% in the experimental arm (vs. 3.6% in the control arm). Although not practice-changing, this trial offered a proof of concept of the potential role of angiogenic inhibitors for maintenance therapy in metastatic pancreatic cancer.

Despite the aggressiveness of this disease may limit the window of opportunity for using a maintenance treatment, a growing interest in this subject is emerging, mainly because of the current availability of more effective multidrug regimens. Metformin, an oral hypoglycaemic agent, may contribute to achieve disease control inhibiting EGFR and m-TOR pathways and, based on preclinical studies, it appears to potentially inhibit pancreatic cancer cell lines as a result, confirmatory clinical trials have provided contradictory results. An ongoing trial is randomizing patients with metastatic pancreatic cancer who have received FOLFIRINOX or a gemcitabine-containing regimen and have responded or achieved stable disease to metformin or metformin plus rapamycin.

Ganitumab (AMG 479), a monoclonal antibody against insulin-like growth factor 1 receptor, was studied as maintenance therapy after combination therapy with gemcitabine and radiation therapy.
resulting in a good and manageable safety profile. However, the negative survival results of phase III trial of gemcitabine plus ganitumab seem to minimize the future role of this compound in this disease.

The molecular classifications of pancreatic cancer could also lead to target new pathways and to extend maintenance options. Whether in the near future new maintenance therapies will be tested in specific molecular subgroups of pancreatic cancer is of extreme interest. Olaparib, a Poly ADP ribose polymerase inhibitor, is currently being studied as maintenance therapy in metastatic pancreatic cancer patients with germline mutation of BRCA 1/2.

MAINTENANCE THERAPY IN HCC

Despite the remarkable worldwide incidence and prevalence of liver cancers, the median survival for patients with the unresectable or metastatic disease is limited to only few months. The reasons for these discouraging results are attributed to the lack of effective treatment options for patients with advanced disease, being sorafenib, a multi-kinase inhibitor that targets vascular endothelial growth factor (VEGFR), the only available evidence-based systemic treatment. However, a press release by Bayer has recently announced that the RESORCE trial testing regorafenib in patients with HCC whose disease had progressed after treatment with sorafenib.

In this general panorama, finding new effective therapies is mandatory for improving survival of HCC. Moreover, it is also necessary to preserve the liver function while arresting the disease evolution. Systemic therapy following interventional procedures may be considered a maintenance therapy. Some authors have analyzed the impact of treating with maintenance interferon (IFN) patients who underwent liver resection or TACE in order to reduce the risk of disease recurrence. A meta-analysis of 10 trials with a total of 1,029 subjects treated with a locoregional procedure, either TACE or surgical resection, compared the outcomes of patients who received IFN after procedure versus placebo only. The recurrence rates of HCC in IFN maintenance group were significantly lower with an odds ratio (OR) of 0.66 (95% CI, 0.50-0.86; p = 0.02), the beneficial effect of maintenance strategy was more evident after TACE (OR 0.54; 95% CI, 0.33-0.86, p = 0.01). Moreover, also the death rates were significantly reduced in the IFN group (OR 0.42; 95% CI, 0.32-0.56; p < 0.00001). Similar results were showed in a later analysis. These data support IFN as a maintenance strategy to reduce recurrence rate and improve survival of HCC after an interventional procedure.

Based on the data demonstrating that procedure such as three-dimensional conformal radiation therapy (3DCRT)/intensity-modulated radiation therapy (IMRT) combined with TACE can improve outcomes in local control and survival of locally advanced HCC, sorafenib has been added to prevent intra-hepatic spread of liver metastases. An ongoing phase I/II trial is enrolling patients to receive TACE plus 3DCRT/IMRT followed by sorafenib at the dose of 400 mg twice a day continuously given for 12 months unless intolerable toxicities and/or tumour progression. Aim of this study is to demonstrate superiority of the addition of sorafenib to the above-cited strategy in terms of time to progression (TTP), PFS, and OS in comparison to historical data. Also, the biological response modifiers (BRMs) have been tested as maintenance therapy for HCC. For example, BRMs were given in combination with 5-FU after percutaneous ethanol injection (PEI), trans-catheter arterial embolization (TAE) or arterial infusion of antitumor agents (AI). However, this strategy did not show to improve outcomes.

Recently, some studies combined standard sorafenib with doxorubicin or gemcitabine. Based on the results of a recent retrospective study focused on the GEMOX regimen (gemcitabine/oxaliplatin) that showed an objective response rate (ORR) of 22% and an OS of 11 months, a prospective study adding sorafenib to this regimen was conducted. In this open-label prospective trial patients with advanced HCC received GEMOX in combination with sorafenib up to 6 cycles and patients without progression where further treated with sorafenib maintenance until disease progression. The ORR registered was 26.5%, median TTP was 10.3 months, and median OS was 15.7 months. The preliminary data suggested that GEMOX plus sorafenib followed by maintenance sorafenib was effective and manageable; however, further confirmatory analyses are required.

Developing maintenance strategies for HCC patients could be important to improve both recurrence-free survival after local treatment and overall survival together with the attempt of preserving hepatic function from the toxicities that may be caused by a prolonged maximal therapy. Most of the maintenance trials address the issue of prolonging the benefit of interventional procedure rather than depotentiating or maintaining the benefit gained with a systemic treatment. The future is exciting, but still we have a long way to go.
CONCLUSIONS

Since the aims of palliative treatment remain to prolong survival, control symptoms and preserve an adequate quality of life, it seems reasonable to stop any intense first-line treatment after 4 to 6 months as long as an adequate disease control has been achieved. Thereafter, a less-intense treatment may be useful to reinforce the clinical results while ensuring an optimal quality of life.

The interest in maintenance strategy, which has been largely adopted in treating colorectal cancer patients with advanced disease, is growing in other gastrointestinal cancers for at least two main reasons. Firstly, maintenance therapy has a more favourable tolerability profile that may favour long-term treatment strategies. Secondly, it may create a window of opportunity for novel drugs to be tested. Still, the future is uncertain, but it looks certainly promising.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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