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Case Report

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Treatment Care Pathways of Four Patients with Metastatic Gastro-Oesophageal Cancer in the United Kingdom (UK), Utilising Trifluridine/Tipiracil

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Abstract

Metastatic gastro-oesophageal cancer outcomes remain poor despite advances in systemic treatment. Clinical deterioration if often rapid and uncontrolled symptoms can affect quality of life. Trifluridine/tipariciI was approved in 3rd line setting after it demonstrated superior median survival compared to placebo. Although treatment is beneficial, not all patients respond to treatment. Here we present treatment journey of 4 patients who have previously received at least 2 lines of palliative systemic therapy, treated in two hospitals in the United Kingdom. We also use clinical parameters to retrospectively determine prognosis based on published clinical prognostic scores.

Keywords

Trifluridine/Tipiracil; Metastatic; Gastric cancer; Esophageal cancer; Gastro-oesophageal junction cancer; Prognosis; Prognostic score

Introduction

Metastatic gastric and gastro-oesophageal junction cancers outcomes remain poor, despite advances in treatment. Five years survival for stage 4 disease is less than 10%, in most parts of the world [1]. Although histopathological classification has little clinical impact, there is evidence to suggest that diffuse type and signet ring tumours do worse [2]. Molecular classification has characterised gastric cancer further, demonstrating different principal driver pathways and prognosis for each subtype [3,4].

Systemic chemotherapy remains mainstay of care in metastatic disease. Choice of first line treatment depends on patient fitness and molecular profile. In first line setting, backbone chemotherapy for most patients comprises of platinum doublet in combination with Trastuzumab in the presence of HER-2 receptor amplification [5,6]. Recently, Pembrolizumab and Nivolumab received approval in first line setting in combination with platinum doublet for tumours with combined positive score (CPS) of ≥10 and CPS ≥5 respectively [7,8]. So far, only Pembrolizumab has received approval in the United Kingdom and Nivolumab is awaiting Medicines and Healthcare products Regulatory Agency (MHRA) approval. Second line treatment options include taxanes, ramucirumab (single agent or in combination with taxanes), or irinotecan [9]. However, amucirumab is not available within the National Health service (NHS). Patients with mismatch repair protein deficiency can still receive immune check point inhibitors in 2nd line (2L) setting onwards, if not already given in first line (1L) [10]. Clinical Prognostic scores in both 1L and 2L settings have been published, to help guide treatment strategy in clinical setting and patient stratification for clinical trials [11-13].

In 2019, Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved trifluridine tipiracil (Lonsurf) for metastatic gastric cancer in 3rd line setting following the TAGS clinical trial. This showed improved overall survival with trifluridine/tipiracil compared with placebo (5.7 vs. 3.6 months respectively) [14,15]. Other approved drugs in 3rd line setting include Nivolumab and Apatinib, licenced in Asia and other countries, but not the UK or Europe [16,17]. Here we present cases of patients who received chemotherapy beyond 2nd line and challenges encountered.

Case Presentation

Patient A

Patient A is a 79-year-old patient, with T4N1M1 metastatic adenocarcinoma of the proximal stomach. He was commenced on trifluridine/tipiracil at 35mg/m^2, twice daily on days 1-5 and 8-12 of each 28-day cycle after 2 lines of therapy. Baseline ECOG Performance status was 1 prior to 3rd line treatment. He tolerated the first 2 cycles well with no side effects. He remained clinically well and treatment was paused due to the 1st wave of the COVID virus pandemic and at this time access to imaging was unfortunately limited to emergencies. Computerised Tomography of Thorax Abdomen and Pelvis (CT TAP) at 5 months (including the 3 months break) from the start of trifluridine/tipiracil showed a mixed response with stable and progressive disease. As the patient was clinically well and performance status maintained, he was re-exposed to trifluridine/tipiracil at the same dose. After further 3 cycles, he had another CT TAP, which showed stable disease. The main side effect from treatment was neutropenia which started after cycle 3. This was managed with Pegfilgrastim 6 mg, subcutaneously and dose intensity maintained. The next CT TAP was delayed due to the 2nd wave of COVID. As he was continuing to get clinical benefit, he continued treatment. CT Scan after cycle 10 showed disease progression. Performance status was still 1. As there were no locally available clinical trials and patient was unwilling to travel out of the region, he was re-exposed to weekly Paclitaxel based on previous good response. Unfortunately, after 2 cycles, CT scan showed disease progression and treatment was stopped. He was then put onto Best Supportive Care pathway.

Patient B

Patient B is a 67-year-old patient with metastatic Her-2+ Gastro-Oesophageal Junction (GOJ) adenocarcinoma. He was commenced on trifluridine/tipiracil 35mg/m^2, twice daily on days 1-5 and 8-12 of each 28-day cycle after 3 lines of chemotherapy (refer to table 1). Baseline ECOG Performance status was 0. Side effects after the first 2 cycles were grade 1 nausea, grade 1 fatigue and reduced appetite. On

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Table 1: Summary of Patients.

Parameters	Patient A	Patient B	Patient C	Patient D
Disease site	Gastric	Type 1 GOJ	Type 1 GOJ	Gastric
Number of metastatic sites at baseline (prior to trifluridine/ tipiracil)	4 (peritoneum, portal vein, distant lymph nodes, pleural effusion	2 (liver, distant nodes)	2 (lungs and distant nodes)	2 (lymph nodes, peritoneum)
Previous surgery	No	No	No	No
Tumour differentiation	Poorly differentiated with focal neuroendocrine differentiation	Moderately differentiated adenocarcinoma	Moderately differentiated adenocarcinoma	Moderately differentiated adenocarcinoma
Molecular markers	HER-2 neg pMMR; NTRK neg	HER-2 pos pMMR, NTRK neg	HER-2 Neg MMR and NTRK not tested	HER-2 neg MMR and NTRKnot tested
Lines of treatment before trifluridine/ tipiracil	2 (F P; T)	3 (FPT; rechallenge with FP; T)	2 (FP/ I)	2 (FP; IF)
Baseline PS prior to trifluridine/ tipiracil	1	0	1	1
Reason for not starting trifluridine/ tipiracil	N/A	N/A	N/A	Rapid clinical deterioration
Number of trifluridine/ tipiracil cycles	10	2	2	N/A
Reason for stopping trifluridine/ tipiracil	Disease progression	Disease progression	Disease progression And upper GI bleeding	N/A
Side effects from trifluridine/ tipiracil	Grade 1 fatigue Neutropenia (<1.0)	Grade 2 Fatigue Neutropenia (1.1)	N/A	N/A
Other treatments	Post trifluridine/ tipiracil re-challenged with Paclitaxel	Radiotherapy 20Gy in 5 fractions for tumour pain	Tranaxemic Acid Radiotherapy not given	N/A
*Time from start of trifluridine/ tipiracil to death	20 months	3 months	8 months	N/A
*Survival from diagnosis	34 months	60 months	18 months	25 months

GOJ- gastro-oeosophageal junction; N/A- not applicable; 5FU-fluorouracil; *- rounded figures; pMMR-proficient mismatch repair proteins; HER-2 -human epidermal growth factor receptor 2; NTRK - Neurotrophic tyrosine receptor kinase; P-Platinum; F-Fluoropyrimidine; T-Taxane; I-Irinotecan; T-Trastuzumab

Table 2: RMHI prognostic score (pre 1st line).

Parameter	A	B	C	D
PS ≥ 2	1 (PS 2)	0	0	0
Presence of liver metastasis	0	0	0	0
Presence of Peritoneal disease	0	0	0	1
ALP>100	1 (113)	0	0	0
Score	**2**	**0**	**0**	**1**
	Moderate	Good	good	good
Response to 1st line	Mixed response (disease progression and partial response)	Partial response	Stable disease	Stable disease

(Scoring: 0-good risk; 1-2 moderate risk; 3-4 poor risk)

week 2 of cycle 3, he was admitted to hospital unwell. He was treated for neutropenic sepsis as per local treatment protocol. CT scan on cycle 3 showed disease progression. He recovered from the sepsis and was discharged home 4 days later. At this point performance status had deteriorated to 3 and clinical condition continued to decline. Treatment was stopped and unfortunately the patient passed away at home 4 weeks following hospital discharge.

Patient C

Patient C is a 58-year-old patient with metastatic HER-2 negative Type-1 GOJ adenocarcinoma. He was commenced on trifluridine/ tipiracil after 2 lines of therapy. Baseline ECOG Performance status was 1. During cycle 1, he presented to hospital with hematemesis and low haemoglobin of 76 (130 g/L-180 g/L). Platelets were within normal range. He was on enoxaparin for pulmonary embolism. Gastroscopy did not show any active bleeding and Enoxaparin stopped. He had the 2nd cycle of treatment but developed further intermittent hematemesis with drop in haemoglobin, requiring blood transfusions. Repeat gastroscopy showed friable tumour, with bleeding on contact with the scope. He was referred for radiotherapy and commenced on Tranexamic Acid. By the time he was reviewed for radiotherapy, bleeding was controlled as evidenced by increase in haemoglobin level, thus decision made not to proceed. He was not able to go back on trifluridine/tipiracil due to clinical deterioration and radiological evidence of disease progression.

Patient D

Patient D was an 80-year-old gentleman with metastatic gastric adenocarcinoma. He was consented for trifluridine/tipiracil after 2 lines of therapy. Just prior to starting treatment he was admitted to his local hospital with E.coli sepsis as a result of cholangitis. Unfortunately, his clinical condition deteriorated rapidly and could not be started on treatment. He was then put on Best Supportive Care (BSC) pathway.

In all four patients, retrospective prognostic scores were done in both 1st and 2nd line settings. (Table 2 and 3). Unfortunately, in the 2nd line setting, none of the patients had been tested for AST and LDH as these do not form part of the routine blood tests panel.

Table 3: RAINBOW/REGARD index score (Pre 2nd line).

Parameter	A	B	C	D
Presence of primary tumour	1	1	1	1
Poor/unknown tumour differentiation	1	0	0	0
Time to progression since prior therapy of <6 months	1	0	1	0
ECOG PS 1	1	0	0	1
Presence of peritoneal disease	1	0	0	1
High ALP level	0	0	0	0
Low lymphocyte level	0	0	0	0
High LDH level	Not done	Not done	Not done	Not done
Low albumin level	1	0	0	0
High AST level	Not done	not done	Not done	Not done
High neutrophil level	0	0	0	0
Low sodium level	1	0	0	0
Score	At least 7 (high)	At least 1(low)	At least 2(low to medium)	At least 3 (medium to moderate)
Response to 2nd line treatment	Partial response	Stable disease	Disease progression	Stable disease

Discussion

All patients presented with metastatic disease and received at least 2 lines of treatment before they were considered for 3rd line trifluridine/tipiracil. All patients received first line platinum doublets and Herceptin in the case of patient B. Although patient A had radiological evidence of disease progression on first lien treatment, ECOG performance status improved from 2 to 1. Second line treatment was either taxanes, or irinotecan based. Patient B was re-challenged with platinum as he had had >3 years good disease control. He achieved stable disease. Three of four patients managed to start on trifluridine/tipiracil at full dose (35mg/m^2) twice daily on days 1-5 and 8-12 of each 28-day cycle.

Patient A received most benefit from trifluridine/tipiracil despite treatment interruptions due to COVID, with survival of 20 months from start of trifluridine/tipiracil until death. In the TAGS trial, over 50% of patients had received at least 3 lines of treatment [15]. The trial protocol included patients whose disease had progressed within 3 months of the last dose of therapy or were unable to tolerate their previous therapy. Over 50% of the whole study population had 3 or more metastatic sites. Post study systemic therapy was given to 25% of patients in both treatment arms. Partial response was 4% with disease control rate of 44% in the trifluridine/tipiracil arm. Time to deterioration of performance status was 4.3 months vs. 2.3 months in the trifluridine/tipiracil and placebo arms respectively. Treatment was well tolerated, with grade 3 or worse adverse events reported in 80% vs. 58%, in trifluridine/tipiracil and placebo arms respectively. The most common grade 3 adverse events were neutropenia (34%), anaemia (19%) and leucopenia (9%). Neutropenia was seen in both patient A and B but not in patient C. The tags and recourse study reported febrile neutropenia in 2% and 4.5% of patients respectively. Neutropenia was associated with treatment benefit in recourse study [18]. Response to treatment and disease control with other 3rd line agents like Apatinib and Nivolumab are comparable to trifluridine/tipiracil, reflecting disease resistance at this stage of the treatment pathway [16,17]. Increasingly, patients who are still fit after 3rd line treatment are referred for further lines of treatment including clinical trials, as observed in the TAGS study.

Although patient B, had the longest survival, he also did not respond to trifluridine/tipiracil. Unfortunately, he died at about 3 months from start of trifluridine/tipiracil despite baseline ECOG performance status of 1 and good response to previous lines of treatment. 16%-20% of patients in the tags study were HER-2 positive. Both HER-2 positive and HER-2 negative patients benefited from trifluridine/tipiracil compared with placebo [15]. Patient C had radiological evidence of disease progression following 2 cycles. He also had intermittent upper gastrointestinal bleeding likely to have been due to combination of disease progression and anticoagulation. Patient D was unable to start treatment due to rapid clinical deterioration following a septic episode.

Patient fitness and disease burden affect outcome in most cancers. The Royal Marsden Hospital prognostic index score (RMHI) which was subsequently validated in the REAL 2 study cohort, reported that presence of peritoneal disease, liver metastasis, and ECOG performance status were significant prognostic factors [11,12]. Pooled analysis of 1,721 patients, showed median survival times for good, moderate, and poor risk groups to be 12.7 months, 8.6 months, and 4.3 months, respectively [11]. One-year survival for good, moderate, and poor risk groups were 48.5%, 25.7%, and 11%, respectively. In addition, patients in the good risk group who achieved good radiological response had better survival in contrast to non-responders, highlighting importance of early disease response. Slightly different Japanese Clinical Oncology Group (JCOG) prognostic index (JCOG index), also showed that ECOG PS ≥1, ≥2 metastatic sites, no prior gastrectomy, and elevated serum Alkaline Phosphatase (ALP), were significant prognostic markers [19]. One year survival in good, moderate and poor prognostic groups were 70%, 40.2% and 19.3% respectively, which was comparable to the RMHI score. Our retrospective analysis of prognostic indices showed that prior to 1st line treatment, Patient A was classified as moderate risk whilst the rest were in the good prognostic groups (Table 2). In 2nd line setting, Fuchs et al identified 12 independent prognostic factors of survival (Rainbow/Regard index score) and came up with a 4-tier prognostic index score (low risk 0-2; medium risk 3-4; moderate risk 5-6; high risk 7-13) [13]. Survival for low, medium, moderate and high risk groups were 14.46 months, 9.92 months, 6.41 months, 3.35 months respectively [13]. Although patient A, is classified as high risk group prior to 2nd line weekly paclitaxel, response to treatment and availability

of 3rd line treatment had a positive impact on outcome (Table 3). Patients B and C classified as low to medium risk group prior to 2nd line treatment did not respond to trifluridine/tipiracil. Unfortunately, at present we do not have clinically meaningful predictive markers to chemotherapy agents.

Choi et al, reported prognostic factors in patients who received 3rd line treatment [20]. Age, chemotherapy regimen and gender were not significant factors for survival. Median time interval of ≥9.5 months from 1L line therapy to 3L was a significant prognostic factor. These patients had better overall survival compared with those with interval of ≤9.5 months. In the post study subgroup exploratory analysis, Tabernero et al, looked for clinicopathological predictive factors to trifluridine/tipiracil [21]. None of the baseline clinicopathological factors analysed on multivariate cox regression analysis, were predictive of overall survival and to date there are no published predictive biomarkers to trifluridine/tipiracil. Nevertheless, superior benefit to trifluridine/tipiracil was observed in 3L compared with 4L setting and beyond. Median survival in 3L setting in the trifluridine/tipiracil group, was 6.8 months compared to 5.2 months in 4+ line; indicating that perhaps trifluridine/tipiracil should be considered earlier in the treatment pathway than later. This is in contrast to what was seen in the RECOURSE study in chemo-refractory colorectal cancers [22,23].

Median overall survival was 5.7 months vs. 4.0 in the trifluridine/tipiracil and placebo arms respectively [22]. Exploratory analysis by prognostic factors showed that patients with low tumour burden, with at least 3 lines of treatment and responses to previous treatment, had better survival than their counterparts [23]. In addition, those in the trifluridine/tipiracil arm without liver metastasis had overall survival of 16.4 months compared to 7.7 months with liver metastasis in the same group.

Uncontrolled symptoms and poor quality of life can interfere with treatment and ultimately survival. Chau et al reported that pre-treatment general wellbeing, role functioning, and global quality of life affect survival [11]. Fuchs et al, also reported that disease related symptoms can adversely affect outcome [13]. Improvements in fatigue, nausea/vomiting, dysphagia and pain have been reported in patients receiving radiotherapy [24]. Most of the data available is retrospective with variable results, thus optimal dose of radiotherapy for symptom control remains unclear [25]. Early involvement of palliative care services is also important for ongoing supportive care.

Conclusion

Trifluridine/tipiracil is effective in 3rd line setting compared with placebo. Absence of predictive biomarkers, like it is the case with other chemotherapy agents makes it difficult to select patients who will receive the most benefit from Trifluridine/tiparicil. Although presence of adverse clinicopathological factors can be predictive of survival outcome, they are not necessarily predictive of treatment response. Disease heterogeneity due to complex underlying molecular landscape, has significant impact on disease response and survival. Therefore, prognostic indices combining molecular markers, host immune factors, gut microbiome and clinicopathological factors are required to properly stratify patients and guide treatment. Further studies are required to help identify patients who might benefit from re-exposure to past treatments.

Disclosures

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