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Research article

Efficacy of A Fluoropyrimidine plus Mitomycin C in Pretreated Patients with Metastatic Colorectal Cancer Eligible for Regorafenib: A Retrospective Study

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Abstract: Objective: In the placebo-controlled CORRECT study, individuals with metastatic colorectal cancer (mCRC) receiving Regorafenib (RGR) achieved significant benefits in both median overall survival (OS: 6.4 months) and progression-free survival (PFS 1.9 months). Patients included in the study had previously failed all standard therapies, which must have included Fluoropyrimidines (FPDs), Oxaliplatin, Irinotecan, Bevacizumab, and Cetuximab or Panitumumab for *K-RAS* wild-type subjects. FPDs plus Mitomycin C (MMC) represent one of the few treatment options for mCRC patients currently eligible for RGR. We wanted to investigate the therapeutic benefit of this pharmacological association in the same clinical setting defined for RGR. **Methods:** We retrospectively evaluated the records of mCRC patients followed in our Institutions that would have fulfilled inclusion/exclusion criteria for the CORRECT trial and received instead the combination of FPDs and MMC. We therefore collected data from 87 patients: 61 fulfilled the criteria required for this analysis. **Results:** Median OS was 9.3 months (95% CI 9.0–15.4), with a median PFS of 3.3 months (95% CI 2.9–3.8). One third of the patients (29.5%) achieved disease control. No significant differences in OS and PFS were found between *K-RAS* WT and *K-RAS*

mutant individuals. Likewise, Performance Status (PS) and the primary site of disease were not associated with differences in response rates. **Conclusions:** These results suggest the need for a prospective study assessing RGR cost-effectiveness compared to FPDs plus MMC for mCRC patients that progress after standard treatments.

Keywords: Colorectal Cancer; Chemotherapy; Mitomycin C; Fluorouracil; Capecitabine; Regorafenib

1. Introduction

Worldwide, CRC is the third most common cancer in men and the second in women [1,2]. At least 50% of patients diagnosed with CRC present with metastatic disease or will develop metastases in the later stages of their illness [3]. Overall survival for mCRC has remarkably improved in the last few years, increasing from 8–12 months to the current 24–30 months [4,5]. Hence, an increasing number of mCRC patients eventually exhaust all available lines of therapy, despite maintaining a good performance status. Finding additional therapeutic options for these patients currently represents an unmet medical need in oncology [2,6].

Previous reports have suggested a role for MMC-based regimens as salvage treatment for mCRC [7–12]. However, the available evidence mostly derives from small retrospective studies or phase II prospective trials published in the pre-targeted therapies era. Thus, the overall data were never considered strong enough to propose the use of MMC, alone or in combination with other therapies, as the standard of care [13,14].

Regorafenib is a novel multi-kinase inhibitor, targeting many signaling pathways that modulate cell survival, proliferation and neo-angiogenesis [15]. Axel Grothey and colleagues have published the results of a multi-centric, randomized, double-blind, placebo-controlled phase III study (CORRECT) assessing the efficacy of this drug for mCRC patients who had previously failed all standard lines of treatment. The study indicated a statistically significant advantage for patients receiving RGR in terms of OS (HR 0.77), PFS (HR 0.49), and disease control rate (41% *vs* 15%, $p < 0.0001$). In spite of the statistical strength of these findings, clinical benefits are limited, with a median improvement of 1.4 months for OS and 0.2 months for PFS [16]. Moreover, treatment-related adverse reactions have been observed in 93% of patients receiving RGR (54% of grade 3–4) and in 61% of the placebo arm. Nevertheless, RGR received FDA approval in September 2012 and is currently considered the standard of care for patients with mCRC that has progressed after FPDs, Oxaliplatin, Irinotecan, Bevacizumab, and Cetuximab or Panitumumab.

We decided to retrospectively review the clinical records of mCRC patients followed in our Institutions that would have fulfilled the inclusion/exclusion criteria of the CORRECT trial and received a combination of FPDs and MMC for their disease.

2. Materials and methods

2.1. Patients and study design

This was an open-label retrospective, observational study. We evaluated patients from 2 Sicilian centers, age ≥18 years, with a histologically- or cytological-confirmed diagnosis of metastatic colorectal cancer, an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, and at least one evaluable tumor lesion according to response evaluation criteria in solid tumors (RECIST) version 1.1. All patients received an FPD plus MMC-based regimen after disease progression despite all standard lines of therapy. Previous treatments had to include: 5-Fluorouracil or Capecitabine, Oxaliplatin, Irinotecan, Bevacizumab, and Cetuximab or Panitumumab if neoplastic cells exhibited wild-type *K-RAS*. Previous therapy with RGR represented an exclusion criterion.

2.2. Treatment protocols

Patients received a 6 or 10 mg/mq MMC bolus on day 1 plus Capecitabine 1000/mq/bid, orally, on days 1–14 of every 21-day cycle. An alternative regimen combined MMC, 10 mg/mq on day 1, with a 48 hour continuous infusion of 5-Fluorouracil (5FU), 1200 mg/mq/day starting on day 1 and 15, plus a Leucovorin (LV) 20 mg/mq rescue, on days 1, 2 and 15, 16 of each 4 week cycle.

Maximum MMC dose allowed was 20 mg per cycle. However, no limiting cumulative dose was pre-specified. The preferred schedule (i.e. infusional 5FU vs oral Capecitabine) was based on patient's preference and compliance.

2.3. Statistical analyses

OS was the primary endpoint and was calculated from the first administration of FPD + MMC until death.

Secondary endpoints were PFS (evaluated from the beginning of treatment until progression or death) and response rate (measured employing RECIST version 1.1) [17].

The Kaplan-Meier method was employed to estimate OS and PFS with 95% confidence intervals (CI).

The log-rank test was used to compare the survival curves of patients with different characteristics. The level of significance was set at 0.05. Statistical analyses were performed using MedCalc.v14.8.1.0.

Patients were also evaluated for performance, *K-RAS*, status and primary disease site. A secondary analysis was also performed to assess possible differences in OS and PFS between patients treated with 5FU + MMC (32, 52% of the total population) and those receiving Capecitabine + MMC (29, 48%).

Toxicities were retrospectively evaluated using Common Terminology Criteria for Adverse Events, version 4.03.

3. Results

Between 2008 and 2014, 87 patients followed by the Medical Oncology wards of our Institutions received an FPD combined with MMC. Sixty-one of them fulfilled the criteria for our analysis. Their characteristics are listed in Table 1. The median number of cycles was 3 (range: 1–12). Statistical analysis of the acquired data showed a median OS of 9.3 months (95% CI 6.9–10.5) with a median PFS of 3.3 months (95% CI 2.9–3.8) (figure 1). Partial remission, stable disease and disease control were achieved in 5%, 24.5% and 29.5% of patients, respectively. No significant differences were found by the subgroup analysis between KRAS WT or KRAS mutant patients. Likewise, PS and the primary site of disease were not associated with differences in response.

Table 1. Patients characteristics.

	Fluoropyrimidine + Mitomycin C (N = 61)
Median age (years)	69.3 (37.2–80.7)
Sex	
Men	38 (62%)
Women	23 (38%)
ECOG performance status	
0	45 (73%)
1	16 (27%)
Primary site of disease	
Colon	41 (67%)
Rectum	19 (31%)
Colon and Rectum	1 (2%)
***KRAS* mutations**	
Absent	38 (62%)
Present	22 (36%)
Unknown	1 (2%)
Previous anti-VEGF treatments*	
Bevacizumab	42 (68%)
Aflibercept	5 (8%)
Both	5 (8%)
Previous treatment lines for metastatic disease	
1–2 §	32 (52%)
3	20 (32%)
≥4	9 (15%)

Patients stopping previous treatment for progression	
Fluoropyrimidine	56 (92%)
Bevacizumab	32 (52%)
Irinotecan	52 (85%)
Oxaliplatin	39 (64%)
Panitumumab, Cetuximab or both	32 (52%)

*patients who had not received anti-VEGF treatment had specific conditions contraindicating anti-angiogenic therapy;

§one patient (2%) received only one previous line of treatment for metastatic disease.

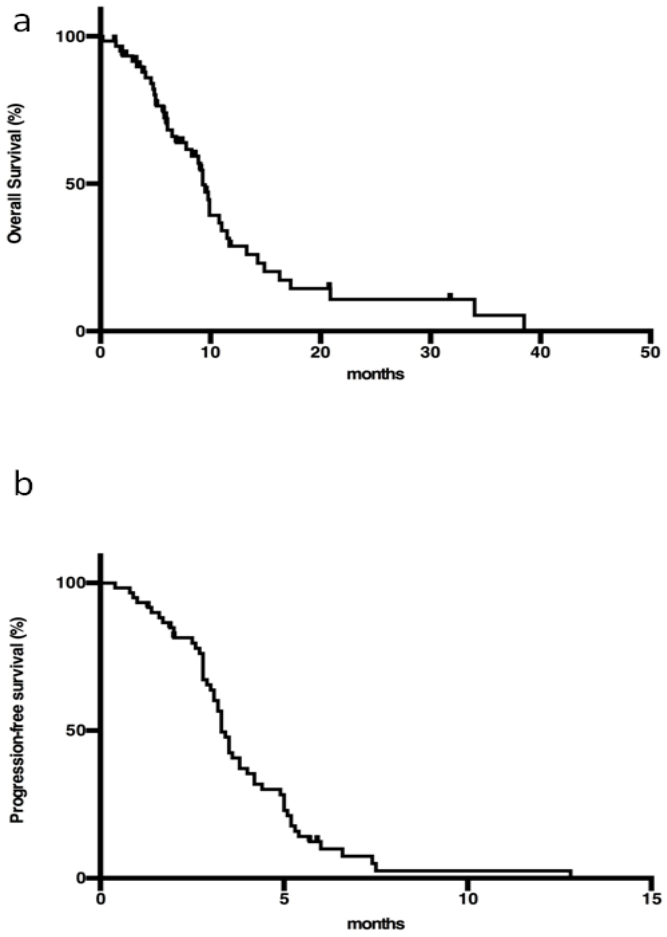

Figure 1. Kaplan-Meier analysis for Overall Survival (a) and Progression Free Survival (b).

A comparison between infusional and oral FDPs showed a significantly better PFS for patients treated with Capecitabine versus those treated with 5FU (5.7 *vs* 3.5 months; HR 0.47; *p* 0.02).

Nevertheless, OS was not significantly different in the two groups (9.9 *vs* 11.7 months; HR 1.03; *p* 0.93).

Overall, 55 patients (90%) developed adverse events of any grade. Anemia (36%), thrombocytopenia (29%) and neutropenia (22%) were the most frequent hematological toxicities. Non-hematological toxicities were mainly fatigue (56%), diarrhea (23%), nausea (19%) and mucositis (15%). Grade 3 adverse events occurred infrequently (9%), while no grade 4 adverse events and toxicities-related death were observed. Seventeen patients (27%) required dose reductions and three (5%) discontinued treatment: one because of persistent thrombocytopenia, one presented grade 3 anemia, requiring blood transfusions and the third one experienced grade 2 diarrhea with dehydration leading to acute renal failure. No cases of hemolytic-uremic syndrome were reported.

4. Discussion and Conclusion

The results of our retrospective study corroborate the efficacy of an FPD plus MMC in heavily pre-treated mCRC patients, eligible for RGR.

In the CORRECT trial, both the primary (OS) and the secondary (PFS) end-point were significantly prolonged by RGR, compared with placebo. Still, the advantage for patients receiving RGR was poor if we look at the overall numbers: compared with the placebo group, RGR-treated subjects gained 1.4 months (36 days) in OS and 0.2 months (6 days) in PFS. We should also consider that the control arm of this trial received no active treatment, but placebo plus best supportive care. Hence, it is likely that the achieved survival data would have been less significant in a study with a control arm containing an active treatment.

Furthermore, RGR has a significant toxicity burden, with 54% of patients in the CORRECT trial experiencing grade 3 or 4 adverse events, and an 8% discontinuation rate due to drug-related toxicities (43/505). The fact that health-related quality-of-life, measured with the EORTC QLQ-C30and EQ-5D scales, was superimposable in the RGR and the placebo groups should not be discounted. However, as Waddell and Cunningham have previously pointed out [5], the tools used to assess this parameter were probably inadequate to properly evaluate the impact of RGR-related toxicities on patient quality of life.

Lastly, the economic burden associated with RGR therapy should not be discarded. Indeed, some concerns have been recently raised about the cost-effectiveness of the drug, with several pharmaco-economic analyses showing a negligible additional benefit, despite a high incremental cost [18–20]. One month of RGR treatment in Italy has an approximate direct cost of 3.000 €.

In our retrospective study we observed survival data that support the use of FPDs + MMC regimens in heavily pre-treated patients. Indeed, OS and PFS were consistent with the most available literature and even superior to some of the available data [7–12].

It should also be noted that patients treated with a combination containing Capecitabine achieved longer PFS compared with the ones receiving 5FU, but the groups displayed no differences

in terms of OS. Thus, a combination with an oral FPD plus MMC should be preferred, even if further studies are still needed to directly compare these two regimens.

The schedules employed in this study displayed an acceptable toxicity profile and, within the limitations of a retrospective trial, we observed a low discontinuation rate of 5% (3/61) suggesting a moderate impact on a patient's quality of life.

Likewise, the proposed chemotherapy regimens are financially reasonable, with variable direct costs, depending on the schedule employed. A raw analysis suggests a 660 € expense per cycle of Capecitabine + MMC.

Our study presents several limits. First of all, it is a retrospective series with a small patient sample. Secondly, there are some foregone discrepancies between our patients and those enrolled in the CORRECT trial. For example, our series included a lower proportion of Bevacizumab pre-treated patients (68%): this difference is easily explained considering that our study includes a real-life population, with a variable incidence of comorbidities contraindicating anti-VEGF treatment.

Moreover, a broader analysis of the current clinical scenario should consider a possible role for TAS-102 (Trifluridine/Tipiracil), a novel oral FPD with proved efficacy in heavily pre-treated mCRC patients. TAS-102 received FDA approval in September 2015 and is currently available in Italy [21]. As the indications for TAS treatment overlap with those for RGR, a concerted effort to assess the best treatment option for this patient population would require a prospective three-arm trial comparing FDP + MMC, RGR and TAS 102.

In conclusion, our study demonstrates that, in a real-life population, the combination of an FPD with MMC is an effective, safe and affordable therapeutic option for mCRC patients that would otherwise be eligible for RGR or TAS-102.

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Conflict of Interest

All authors of this paper declare no conflicts of interest.

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