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Analysis of first-line treatment in older patients with metastasic colorectal cancer

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Abstract

Objective: The purpose of this study was to analyse the effectiveness and safety of first-line treatment of metastatic colorectal cancer (CRCm) in older patients treated in a tertiary hospital.

Material and methods: This was an observational and retrospective study, including patients aged 75 years or older, with CRCm, who received chemotherapy treatment in 2017. The main variables studied were type of treatment, Progression-Free Survival (PFS), Overall Survival (OS), dose reductions, and treatment delays due to adverse events.

Results: A total of 59 patients (71.2% men) with a median age of 76 years were enrolled in this study. About 70% presented colon cancer, with the left colon being the most frequent location. They were treated with 9 different schemes, in most cases using polychemotherapy and biological agents. The median PFS and OS was 12 and 30 months, respectively. A total of 23/59 of patients started treatment at doses lower than recommended in the clinical practice guidelines. In terms of safety, 34/59 of patients had at least one dose reduction, and 30/59 suffered one treatment delay. The most frequent adverse reactions were asthenia, peripheral neuropathy, diarrhoea, and palmoplantar erythrodysesthesia.

Conclusion: Our patients presented baseline clinical characteristics similar to the general adult population, with no tumour characteristics associated with advanced age. The efficacy and toxicity were similar to those in the clinical trials, although our patients had more dose reductions. Considering the heterogeneity of patients and in the absence of clinical trials in the older population, real-life studies can be very useful.

Keywords

Older adults, colorectal cancer, treatment, safety, effectiveness

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Introduction

Globally, colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer death. According to estimates from the International Agency for Research on Cancer in 2018 CRC constituted approximately 1.8 million new cases worldwide.[1] The tumour is becoming especially prevalent in the older population, mainly because of the elevated age at diagnosis and the increased incidence rates in the seventh and eighth decades of life. About 70% of patients affected by this neoplasm in the

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Western world are over 65 years old, and, particularly in Europe, 40% are over 74 years old.[2]

Mortality due to CRC is high, reaching 10 deaths per 100,000 inhabitants per year.[3] It is one of the leading causes of cancer-related death in older patients. However, this group of patients tends to be underrepresented in clinical trials and not adequately treated in clinical practice.[5] In the most relevant studies conducted in patients with CRC, less than 20% of patients were over 70 years old.[4–6]

Approximately 45-55% of tumours are located in the rectum, 35-45% in the ascending and transverse colon, and 5% in the descending colon.[7,8] About one-fifth of the patients had metastases at diagnosis. More than half of patients diagnosed in the early stages of the disease will develop metastases, with the liver and lung locations being the most common.[9]

There are various risk factors that increase the likelihood of this disease. Age is one of them, increasing the incidence of CRC every decade of life above 40 years.[3] Genetic and environmental factors also have an influence.[10]

The initial therapeutic approach to metastatic disease varies depending on the patient's condition, comorbidities, and associated biomarkers, as well as the number and location of metastases, the main objective being to improve the quality of life and, as much as possible, extend the life of the patient. For this, it is necessary to obtain responses that permit surgery for metastases and maintain an adequate general condition that allows for the administration of the different drugs available with the least toxicity. The treatment of metastatic CRC (CRCm) is based primarily on the use of fluoropyrimidine-based chemotherapies (capecitabine or fluorouracil with folinic acid) in combination with irinotecan and oxaliplatin, adding targeted therapies (bevacizumab, ramucirumab, and aflibercept; cetuximab, and panitumumab; regorafenib).[11,12]

In general, the median overall survival (OS) of these patients without treatment is only 5 to 6 months. The incorporation of 5-fluorouracil into treatment allows for doubling the life expectancy of patients. Currently, the use of doublets based on 5-fluorouracil with oxaliplatin or irinotecan has increased response rates by nearly 50%, with median OS of 18-24 months.[11]

The use of assessment scales that discriminate the degree of fragility of the patient for chemotherapy treatment has not yet been extended to the care of older patients diagnosed with cancer. For this reason, this group of patients is often considered not suitable for treatment, or, in many other cases, treatments are prescribed to patients who are very fragile, therefore causing significant side effects due to their toxicity. The use of combined schemes is avoided, and modified regimes, derived from conventional treatments, are offered according to a series of criteria linked to ageing.[13,14]

The main objective of the study was to describe the characteristics of patients with CRCm aged 75 years or older, as well as to determine the effectiveness and safety of the treatments.

Material and methods

The present retrospective, observational, single-centre study was conducted in a third-level hospital. The population under study included all patients aged 75 years or older with CRCm who received chemotherapy from January 2017 to December 2019. The data were collected from the outpatient-dispensing module of the Farmatools® program, the Oncowin® cytostatic prescription software, and medical records.

Demographic variables were sex and age at diagnosis. Clinical variables were location of the tumour and metastases, presence/absence of metastases at diagnosis of the disease, degree of tumour differentiation, ECOG functional status, RAS mutational status, and initial-nadir CEA level. Treatment variables were percentage of patients with tumour surgery and metastasis, rescue surgery, type of drug regimen, reduction of starting dose, and number of cycles administered. Effectiveness was measured as progression-free survival (PFS), overall survival (OS), percentage of responses achieved, measures according to RECIST criteria, and rescue surgery. Regarding safety, the percentage of patients whose dose was reduced and who experienced delays or interruptions in treatment, more relevant adverse effects, and severity, measured according to the standards of the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE), was analysed.

For the data analysis, a descriptive analysis was made of the demographic and clinical variables of the study population, as well as the treatment, effectiveness, and safety variables of the therapies. The continuous variables with normal distribution were reported in terms of their mean and standard deviation. The remaining continuous variables were described according to their median and interquartile range. Categorical variables were listed using frequencies and proportions. The Kaplan-Meier method was used to estimate the PFS and OS, and the comparison between curves was carried out using the log-rank hypothesis test.

All information was treated as confidential and exclusively used in a professional setting. The study participants were identified only by a code in all reports and data analyses. This study was approved by the Aragón Clinical Research Ethics Committee (CEICA).

Results

In 2017, the number of patients who were under treatment for CRC was 46,665 (13.9%) of whom had CRCm and were diagnosed with metastatic disease at 75 years or older. Of the 65 patients, 59 cases were analysed. The remaining six patients could not be included due to lack of data in their medical history. Regarding gender, 42 were men (71.2%) and 17 were women (28.8%). The median age at diagnosis of metastatic disease was 76 years (range 75 to 84 years). A total of 16/59 patients were over 80 years old.

Regarding the tumour location, 41/59 of the patients presented colon cancer, the left colon being the most frequent location, followed by the right colon (Figure 1). If we analysed the sexes separately, left colon cancer prevailed in men (17/42) (Table 1). The ECOG performance status at diagnosis was grade 0 for 28/59 of patients, grade 1 for 26/59, and grade 2 for the remaining 5/59. The median value of the CEA at baseline was 9.3 ng/ml (range 1.2-856.0), and the median of the lowest CEA or nadir value was 4 ng/ml (range 0.8-901.0).

Of the total of patients, 39/59 presented metastases at the time of diagnosis of the disease, and the rest metastasized later. Regarding the location of the metastases, 26/59 of the metastases were hepatic, 11/59 pulmonary, 9/59 hepatic and pulmonary, and 13/59 in other locations. All the tumours were classified as adenocarcinoma, of which 38/59 were well-differentiated (G1-2), 14/59 poorly differentiated, and 7/59 undetermined (Gx); 52.8% (28/53) presented mutation in RAS.

Most patients (33/59) were treated with onset surgery, of which 24 were from the primary tumour, eight from primary tumour metastasis, and one from metastasis. A total of 15/59 patients were rescued to surgery.

The patients were treated with 9 different treatment schedules (Table 2), 50/59 in combination with two or more drugs and 9/59 in monotherapy with capecitabine. The median of administered cycles was 10. Of the patients, 34/59 were treated with oral fluoropyrimidine (capecitabine) versus 25/59 with intravenous fluoropyrimidine (5-fluorouracil). Concerning the second treatment drug, 35/59 of patients also received oxaliplatin-based schemes. A total of 36/59 patients were treated with target therapies (bevacizumab, cetuximab, panitumumab). According to the prescribed doses, 23/59 of patients started treatment at lower doses, in at least one of the drugs, as compared to the recommended doses based on clinical practice guidelines.[11] The reduction percentage reached 20. The response, measured according to the RECIST criteria, was complete (CR) in 6/59 of patients, partial (PR) in 29/59, stable disease (SD) in 17/59, and progression disease (PD) in 7/59.

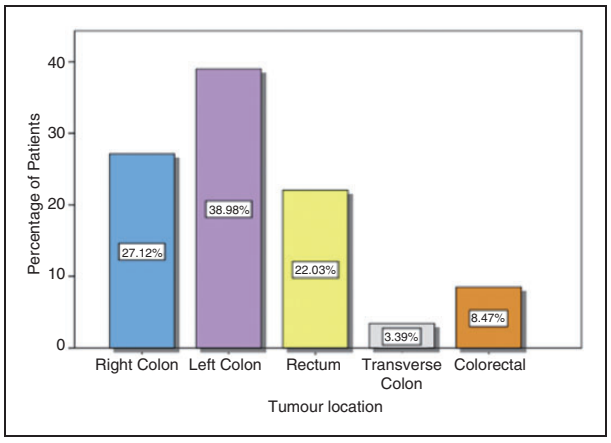

Figure 1. Percentage of patients according to anatomical location.

Table 1. Percentage of patients according to anatomical location and sex.

	Man	Woman	Total
Right colon	10 (23.0%)	6 (35.3%)	16
Left colon	17 (40.4%)	6 (35.3%)	23
Rectum	8 (19.0%)	5 (29.4%)	13
Transverse colon	2 (4.7%)	0	2
Colorectal	5 (11.9%)	0	5
Total	42 (100.0%)	17 (100.0%)	59

Table 2. Frequency of use of the different treatment schemes.

Treatment scheme	n (%)
Capecitabine	9 (15.3%)
Capecitabine + Bevacizumab	12 (20.3%)
Capox	9 (15.3%)
Capox + Bevacizumab	5 (8.5%)
Folfox	5 (8.5%)
Folfox + Bevacizumab	7 (11.9%)
Folfox + AntiEGFR	9 (15.3%)
5-Fluorouracil + Bevacizumab	2 (3.4%)
Folfiri + Bevacizumab	1 (1.7%)
Total	59 (100.0%)

Capox: capecitabine + oxaliplatin; Folfiri: 5-fluorouracil + irinitecan + folinate; Folfox: 5-fluorouracil + folinate + oxaliplatin.

A median PFS 12.16 (2.85-72.00) months was obtained. No statistically significant differences were observed between the PFS medians according to sex, tumour location, metastases location, degree of tumour differentiation, RAS, ECOG, initial surgery and rescue surgery (Table 3).

Table 3. Calculation of SLP and SG (months) achieved by the Kaplan-Meier method based on demographic and clinical variables.

Demographical and clinical variables		SLP median	P[a]	SG median	
Sex	Man	12.07	0.291	29.31	0.096
	Woman	16.46		62.88	
Tumour location	Colon	12.13	0.967	32.79	0.683
	Rectum	12.16		28.85	
Tumour location	Right colon	9.77	0.104	18.42	0.034
	Left colon	17.14		42.69	
Metastases location	Hepatic	12.16	0.238	32.79	0.314
	Pulmonary	47.28		74.58	
	Hepatic and pulmonary	8.00		47.30	
	Other	17.67		35.73	
Degree of differentiation	G1 + 2	16.46	0.940	37.082	0.029
	G3 + 4	12.07		17.67	
RAS mutation	Yes	15.21	0.066	27.14	0.014
	No	11.56		42.69	
ECOG	0	17.16	0.140	33.08	0.250
	1	12.07		30.49	
	2	9.18		11.87	
Surgery	Yes	17.67	0.250	30.48	0.749
	No	11.41		28.85	
Rescue with surgery	Yes	17.48	0.197	41.28	0.009
	No	11.41		28.20	

[a]Calculation using the Long-Rank Test.
ECOG: Eastern Cooperative Oncology Group.

Regarding OS, the median was 30.49 (3.10-81.80). No statistically significant differences in OS were observed based on sex, location of metastases, ECOG and onset surgery. However, there were statistically significant differences depending on whether the patient had undergone rescue surgery or not, location of tumour (right or left), RAS mutation, and degree of tumour differentiation (Table 3). We observed that patients with left colon tumour, no RAS mutation, tumours with degree of differentiation of 1 and 2 (well differentiated), and patients rescued by surgery had better OS (Figure 2).

Regarding drug doses, no statistically significant differences were observed in PFS depending on whether the patient started with reduced doses compared to starting with full doses (12.06 vs 12.16, $p = 0.903$), nor in OS (28.85 vs 33.08, $p = 0.932$). No statistically significant differences in PFS and OS were found either depending on whether the patient suffered a dose reduction due to toxicity or not (PFS: 12.16 vs. 12.16, $p = 0.430$; OS: 33.08 vs. 30.06, $p = 0.614$ respectively).

There was a dose reduction of at least one of the drugs in 34/59 of the patients; the average reduction percentage reached was 14.9%. About half of the patients (30/59) suffered delays in treatment cycles, and one-third of the patients discontinued at least one dose of a drug.

Table 4 shows the most common adverse effects recorded in the medical history and their severity levels, according to the CTCAE classification. The most frequent adverse reactions were asthenia, peripheral neuropathy, diarrhoea, and palmoplantar erythrodysesthesia.

Discussion

Regarding the characteristics of our population, the median age of diagnosis was 76 years, similar to other studies carried out in older patients.[15] According to European literature data, the male/female ratio for CRC is 1.5/1.[16] However, in our study, we found a much higher ratio (2.46/1). This discrepancy could be due to the small size of the population studied. All the patients presented an ECOG less than or equal to 2. These results confirm proposed ESMO practice guidelines, according to which patients with type ECOG 3 would not be candidates for chemotherapy treatment, requiring only symptomatic control.[17]

The most frequent location of the primary tumour was the colon, which coincides with studies carried out both in the general population and in older patients.[12,15,17] One aspect that is increasingly important is the location of the tumour within the colon. In our study, tumours located in the distal colon (left side) were more frequent than those located in the proximal

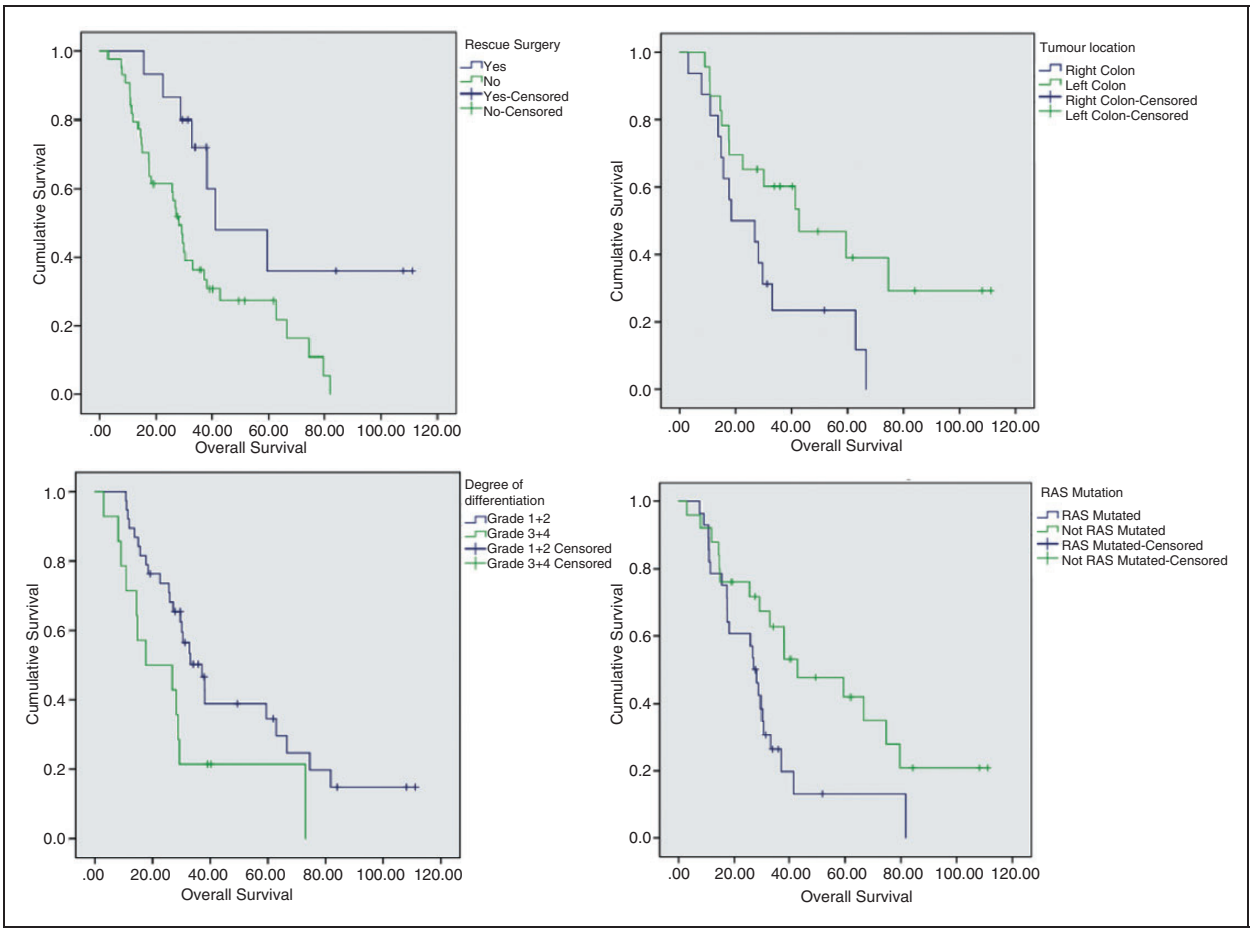

Figure 2. Survival functions.

Table 4. Most frequent adverse effects and their degrees.

Adverse effect	G1+G2	%	G3+G4	%	Total (N = 59)
Asthenia	40/45	88.9	5/45	11.1	76.3%
Peripheral neuropathy	44/44	100.0	0/44	0.0	74.6%
Diarrhoea	25/34	73.5	9/34	26.5	57.6%
PPE	31/33	93.9	2/33	6.1	55.9%
Mucositis	19/19	100.0	0/19	0.0	32.2%
Neutropaenia	11/18	61.1	7/18	38.9	30.5%
Skin drought	14/16	87.5	2/16	12.5	27.1%
Anaemia	13/14	92.7	1/14	7.1	23.7%
Skin rash	8/9	88.9	1/9	11.1	15.2%
Thrombocytopenia	7/9	77.8	2/9	22.2	15.2%
Epistaxis	6/7	85.7	1/7	14.3	11.9%
Nausea and vomiting	5/5	100.0	0/5	0.0	8.5%
Bowel perforation	0/3	0.0	3/3	100.0	5.1%

PPE: palmo-plantar erythrodysesthesia.

colon (right side), which disagrees with the existing data.[18,19]

According to the available evidence, tumours originating on the left side have a better prognosis than those on the right side,[20] so our population had a better prognosis of the disease. Regarding the location of the metastases, 40% of the patients in our population presented liver metastases, being the most frequent location, which coincides with data described extensively in the literature.[8]

One of the most important aspects in the selection of treatment is the determination of the RAS mutational status, because patients with mutated RAS are not suitable for treatment with anti-EGFR drugs, which limits treatment options. In our population, 53% presented mutation in this proto-oncogene. Lund CM et al. conducted a study in older patients and obtained similar rates of EGFR[15] mutation, rates that in turn resembled those of other studies developed in the adult population.[21]

Regarding the type of antineoplastic treatment, the choice of treatment scheme was adjusted to the proposals in the clinical practice guidelines.[11] The ESMO guidelines classify patients with advanced or metastatic disease as fit or unfit. Fit patients would be treated with all available therapeutic options, regardless of age, while unfit should be treated with reduced doses or lower toxicity treatments, or only supportive measures when the clinician considers the patient unfit for recovery. These guidelines recommend the use of oxaliplatin-based doublets (Folfox or Capox) or irinotecan as a first-line treatment. In fragile or unfit patients, considered unfit for these treatments, the use of monotherapy schemes that may be less aggressive for the patient is recommended.[11] The DISCO study, conducted by Lund et al., also performed in patients with CRCm, showed that patients older than 75 years were more likely to receive monotherapy (OR = 1.89, 95% CI 1.28–2.78) and lower doses (OR = 4.34, 95% CI 2.94-6.25) than younger patients. In our study, 15.3% received monotherapy-based schemes, and 39.0% started treatment at lower doses.

Approximately 60% of our older patients were treated with schemes based on targeted therapies, data similar to those obtained by Y Liang et al. in a study conducted in octogenarians, where 57.9% of their study population was treated with these drugs.[22] Although the treatment is well tolerated, few studies are available on this type of population. In addition, a recent systematic review[23] analysed the percentage of inclusion of older and fragile patients in clinical trials of targeted therapies. The authors concluded that the results of randomized controlled trials related to targeted therapies can only be extrapolated to older patients when relevant comorbidities are absent.

Regarding effectiveness data, the median PFS was 12 months, similar to that obtained by Escolano et al., for the general population.[24] However, the median OS of our study was 30.49 months; these results are superior to those obtained in other studies, where the median of OS was 18-24 months.[11] This greater survival might be related to the high proportion of tumours located on the left side, which have better prognosis.

The low sample size did not allow us to find statistically significant differences in the PFS of any of the clinical and demographic variables. However, other studies, such as that of Escolano et al., conducted in the general population, found differences in PFS depending on whether the patient was surgically rescued or not (14 vs. 9, $p = 0.022$) and degree of tumour differentiation (20 months [grade 1] vs 10 months [grade 3], $p = 0.03$). Although Escolano et al. failed to see differences in PFS depending on the RAS mutation, they observed a tendency towards greater survival in patients with non-mutated versus mutated KRAS (13 vs. 10, $p = 0.058$).

Regarding OS, the results showed differences depending on whether or not patients were rescued from surgery. This finding suggests that surgical rescue is one factor leading to improved survival of these patients. A higher OS has also been noted in patients who had non-mutated RAS. This is because tumours with an RAS mutation have a higher rate of proliferation, meaning that the cell is continuously sending proliferation signals to the nucleus.

Our data reflect that patients with a degree of differentiation of 3 and 4 had a lower OS than those of grade 1 and 2 (well differentiated). The degree of differentiation of the tumours is one of the key factors that influence the prognosis of the disease, the poorly differentiated tumours showing a worse disease prognosis.

The study revealed that tumours located in the left colon presented a higher OS than tumours in the right colon. Regarding the tumour laterality and the prognosis of the disease, there are several factors that could have an influence, such as negative expression of the caudal type 2 homeobox transcription factor and high levels of C-reactive protein. These factors have been found to increase the incidence of right-sided CRCm versus left-sided colon cancer. Wang CB et al., who conducted a study with 26,908 patients and 45 years of follow-up, also found that tumours localized in the left colon presented a higher OS (87.5 vs. 76.6 months, $p < 0.0001$).[25]

In our study, the intensity of the initial dose of the drug did not translate into differences in PFS and OS. In the study by Lund et al., reducing the initial dose was only significantly associated with a shorter OS.[15]

Regarding tolerance to the treatments, in our study, there was a reduction in the dose of at least one of the drugs by 57.6%; these results were higher than those obtained by Escolano and others for the general population (31.6%). The safety profile, measured by the number of adverse events, was similar to that obtained by Escolano et al.[24]

One of the main limitations of our study is the small size of the study population.

The strict selection criteria, covering only patients aged 75 and over, made it challenging to enlarge the

sample size. The lack of unanimity in defining the age range that determines an older patient rendered the comparison more difficult. The importance of this work lies in the poor evidence available on the treatment of CRCm in older patients.

Based on the results, we can conclude that our population had clinical baseline characteristics comparable to the adult population, suggesting that there are no typical tumour conditions in older patients. Efficacy and toxicity were similar to those of the clinical trials, although our patients had more dose reductions.

The high prevalence of CRCm in older patients leads to the need to conduct research without excluding patients due to their age or fragility. Considering the heterogeneity of patients and in the absence of clinical trials in the older population, real-life studies can be very useful.

Declaration of Conflicting Interests

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