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Second-Line Chemotherapy of Advanced Colorectal Cancer: Predictive and Prognostic Factors

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Colorectal cancer progression presents a significant clinical problem. After its dissemination, the foundation of its treatment comprises of palliative chemotherapy.
Objectives. The aim of this study was to assess the predictive and prognostic value of clinical response to second line treatment (with capecitabine or with a two-drug regimen including irinotecan) and to analyze its relation to selected clinical and pathological variables with respect to time to disease progression.
Material and Methods. The retrospective analysis of 164 patients with advanced colorectal cancer treated in 2001–2008 included chosen clinical, pathological and follow-up data.
Results. Response to second-line chemotherapy was observed in 34 out of 164 patients: In 18/82 in the irinotecan group (22%) and in 16/82 in the capecitabine group (19.5%). The mean survival time to progression following the second line of treatment amounted to 5.85 and 6.2 months respectively. Statistically, a higher number of patients in good condition of 0 to 1 was documented in the group responding to treatment. Significant correlation was documented between primary stage of the disease and time to progression in patients treated with capecitabine ($p = 0.0258$). The recurrence of the disease was observed in 44/45 patients following operation with radical intention but with an insufficient number of excised lymph nodes. A significantly longer time to progression was observed in women treated with capecitabine. In logistic regression, lack of treatment response was found to be an independent factor affecting the time to disease progression. Patients who did not respond to the second line of treatment demonstrated a significantly shorter time to disease progression than patients who responded to it and they showed a significantly higher number of patients with leucopenia during treatment.
Conclusions. Clinical response to treatment in both treated groups is of significant importance for the probability of local recurrence of the disease, preservation of a good patient's condition and the higher level of leukocytes during treatment (**Adv Clin Exp Med 2016, 25, 4, 725–732**).

Key words: colorectal cancer, adjuvant chemotherapy, predictive factors, therapeutic response, time to progression.

A growing incidence rate (at present reaching about 14,500 cases annually in Poland), frequently long periods of asymptomatic development and a five-year survival index below 50% makes colorectal cancer a significant clinical problem. In advanced stages of the disease, the principal therapy is palliative chemotherapy. Recognizing and applying new, potential prognostic factors may result in better qualification of patients to treatment, improved results and a decreased toxicity. In search of the potential for better clinical response to treatment, we hope to be able to prolong the time to disease progression after the second line of treatment (capecitabine, two-drugs regimen with irinotecan) in advanced colorectal cancer. The aim of the study was to evaluate predictive and prognostic suitability of selected clinical and pathomorphological factors.

Material and Methods

The retrospective analysis included 164 patients observed during 8 years (2001–2008). Two groups of 82 patients, each with histologically ad-

vanced colorectal cancer, (local relapse and/or distant metastases) were evaluated. In patients who were first subjected to a radical operation but requiring adjuvant chemotherapy treatment with fluorouracil, folinate modulation was applied. First line treatment of recurrent disease included fluorouracil with folinate modulation and second line treatment consisted of a two-drug regimen (irinotecan and fluorouracil with folinate modulation) or capecitabine in monotherapy. Analysis of prognostic and predictive significance manifested by selected factors was conducted on the basis of standard medical documentation. Clinical variables were taken into account (primary location of tumor, stage of the disease, radicality of primary surgery, type and site of recurrence or dissemination, age, sex, past medical history, side effects of treatment and drug toxicity) and malignancy grade (G). The group included 93 men (56.7%) and 71 women (43.3%). The group of irinotecan included 47 men (57.3%) and 35 women (42.7%), the group of capecitabine comprised of 46 men (56%) and 36 women (44%). The mean age of the patients (irinotecan vs capecitabine) was 61 and 67.6 years, respectively (in the entire group of 164 patients: 64.3 years). Median age was 54.5 and 69 years, respectively. The primary lesion in the irinotecan group was found in the rectum in 38 out of 82 patients (46.4%), in other locations in 44 patients (53.6%), in the capecitabine group the primary lesion was in rectum in 30 out of 82 patients (36.6%), in other locations in 52 patients (63.4%). In either of the treated groups local recurrence was less frequent than dissemination of the process.

Two regimens of multidrug chemotherapy and monotherapy with capecitabine were applied: 1. Fluorouracil 425 mg/m^2 + calcium folinate 20 mg/m^2 – × 5 days, every 28 days; 2. Capecitabine – 2 × 1250 mg/m^2 – × 14 days, every 21 days; 3. Irinotecan 180 mg/m^2, (fluorouracil 200 mg/m^2 bolus, 400 mg/m^2 infusion) days 1 + 2, calcium folinate 200 mg/m^2 – × 2 days, every 21 days.

Results

Altogether, the second line therapy induced a response in 34 out of 164 patients (20.7%), including 18 out of 82 patients (22%) in the irinotecan group and 16 out of 82 patients (19.5%) in the capecitabine group. No statistically significant difference was noted in the distribution of chemotherapy type (irinotecan, capecitabine) between the patients with a response to treatment and those with progression ($p = 0.847$).

The mean survival time before the manifestation of progression during the second line of treatment in patients receiving irinitecan and capecitabine amounted to 5.85 and 6.2 months, respectively.

In the group treated with irinotecan, the longest time to disease progression was observed in the group of WHO performance score 1 (39 patients) and in the group treated with capecitabine with WHO performance score 1 and 2 (34 patients).

Statistical analysis demonstrated that the distribution of patient performance status following treatment (irinotecan and capecitabine) differed significantly in correlation to the response to treatment ($p \leq 0.00001$). During treatment, 2 and 8 patients died in respective groups. Logistic regression analysis allowed us to demonstrate that patient performance score represented an independent variable affecting response to treatment. Detailed data for predictive value of the analyzed parameters are presented in Table 1.

Statistical analysis failed to demonstrate differences in response to second line chemotherapy with respect to primary lesion location ($p = 0.563$) or differences in time to disease progression during second line chemotherapy between the groups (patients treated with irinotecan or capecitabine) with respect to primary location of the tumor in the colon, rectum or sigmoid colon ($p = 0.483$).

Evaluation of the impact of primary surgery radicality on the results of second line chemotherapy (radical tumor excision in 45 out of 164 patients) showed that time to disease progression was found to be longer in both chemotherapy groups with radical excision. According to the statistical analysis, evaluating the patients treated with irinotecan and patients treated with capecitabine, the patients with response, as compared to patients with progression, were found to consist slightly more frequently of the patients who underwent complete resection ($p = 0.0591$).

All patients with primary disease stage I–III were surgically treated with radical intention. The patients treated with capecitabine and irinotecan included, respectively, 29 and 16 patients (females: 11 and 7 patients, males: 18 and 9 patients). The mean age of female patients amounted to 69 years, the mean age of male patients was 46.9 years. No statistical significance was found in the analysis of the time to disease progression following second line chemotherapy, against the primary stage of disease (I–III vs IV). According to the statistical analysis, the time to disease progression, as compared to the original stage of the disease, conducted separately for the two groups of patients (treated with irinotecan and those treated with capecitabine), a significant difference was detected at the level of $p = 0.0258$ in the group treated with capecitabine.

Table 1. Predictive value of certain parameters of clinical response

Evaluated parameter	Therapeutic response (categories 1 + 2 + 3)	Therapeutic response (category 4)	X2	Df	p
Parameters related to tumor					
Primary localization: intestine, sigmoid colon, rectum	16/5/14	51/29/52	1.15	2	0.563
Malignancy grade G 1/2/3	5/26/3	22/87/8	0.41	2	0.816
Primary tumor size T 1/2/3/4	0/1/16/13	1/3/44/66	2.46	3	0.482
Lymph nodes N 0/1/2	8/8/2/2	19/32/14/11	2.19	3	0.534
Metastases M 0/1	15/19	62/67	0.05	1	0.828
Dissemination					
Liver 0/1	17/17	71/59	0.08	1	0.773
Lung 0/1	26/4	118/12			0.504F
Ovary 0/1	29/1	127/3			0.568F
Other 0/1	29/1	123/7			1.0F
Therapeutic response and patient performance status					
Therapeutic response after first line treatment (1+2+3 WHO category)	12/18	60/70	0.17	1	0.684
Therapeutic response after first line treatment (irinotecan and capecitabine)	18/16	64/66	0.04	1	0.847
Performance status after LF 0/1/2/3	8/21/4/1	19/73/36/2	4.54	3	0.209
Adverse effects					
Diarrhea 0/1/2/3	29/5/2/0	96/25/7/2	1.17	3	0.760
Hand-foot 0/1/2/3/4	31/3/0/0/0	117/6/3/2/1	2.43	4	0.657
Nausea/vomiting 0/1/2	32/2/0	114/11/5	1.66	2	0.436
Mucoses 0/1/2	30/3/0	110/18/2	1.09	2	0.580
Parameters assessed before treatment; pre-existing conditions					
Hemoglobin before 0/1/2	31/2/1	97/22/11	4.31	2	0.116
Platelets before 0/1	32/2	126/4			0.605F
Leucocytes before 0/1/2	34/0/0	128/1/1	0.53	2	0.767
Granulocytes before 0/1/2	34/0/0	129/1/1			1.0F
Lymphocytes before 0/1/2/3/4	20/6/5/2/0	72/32/12/13/1	2.18	4	0.703
Bilirubin before 0/1/2/3	33/1/0/0	115/11/2/2	2.39	3	0.496
TRA before 0/1/2	31/3/0	110/19/1	1.07	2	0.586
Creatinine before 0/1/2	32/2	123/7			1.0F
Glucose before 0/1	26/6	88/39	1.26	1	0.262
Heart diseases 0/1	31/3	103/27	1.84	1	0.175
Hypertension 0/1	27/7	94/36	0.38	1	0.536
Strokes 0/1	34/0	126/4			0.581F
Circulation total 0/1	25/9	89/41	0.13	1	0.717
Bone marrow capacity (hgb, gran., plt.) 0/1	30/4	126/4			0.581F

Table 1. Predictive value of certain parameters of clinical response (cont.)

Evaluated parameter	Therapeutic response (categories 1 + 2 + 3)	Therapeutic response (category 4)	X2	Df	p
Diabetes 0/1	28/6	91/39	1.49	1	0.222
Chronic kidney failure 0/1	32/2	123/7			1.0F
Other neoplasms	34/0	129/1			1.0F
Chronic liver diseases/cirrhosis 0/1	31/3	109/21			0.415F
Parameters assessed during treatment					
Haemoglobin during treatment 0/1/2/3	24/7/2/1	67/32/26/4	5.07	3	0.167
Platelets during treatment 0/1/2/3	30/3/0/1	121/7/1/0	4.65	3	0.199
Lymphocytes during treatment 0/1/2/3/4	5/8/10/9/2	32/26/43/24/4	2.87	4	0.580
Bilirubin in treatment 0/1/2/3/4	30/3/0/1/0	94/20/4/7/3	3.85	4	0.427
Creatinine in treatment 0/1/2	28/4/0	100/23/3	1.46	2	0.481
Glucose in treatment 0/1	14/6	56/29	0.01	1	0.930

In 27 (60%) out of 45 patients primarily operated with radical intention, lymph nodes were not excised or they were not described in the pathomorphology report. Lymphadenectomy with an excision of at least 12 lymph nodes was performed in only one out of 45 patients. The lowest number of excised lymph nodes was removed from the region of rectum, sigmoid colon and colon, successively. Statistical analysis demonstrated no relationship between the number of removed lymph nodes and the response to treatment ($p = 0.534$).

Statistical analysis of the effect of age at the time of diagnosis demonstrated no age-related significant differences in the response to treatment. A more advanced age of patients did not negatively affect the time to disease progression.

Statistical analysis of the time to disease progression demonstrated a prolonged time in women subjected to chemotherapy using capecitabine ($p = 0.0278$) and in the group of women and men evaluated together in the two therapeutic groups ($p = 0.0462$). The mean age of women primarily operated with radical intention and treated with capecitabine was higher by 22.1 years than that of women treated with irinotecan, while the period before relapse of the disease following primary treatment was shorter (it amounted to just 11 months), while the average patient performance score amounted to 1.18, clearly lower than in the group treated with irinotecan.

The time period from progression until local recurrence or metastases in liver or lungs was clearly more prolonged in patients treated with capecitabine. In both groups (irinotecan and capecitabine) the time till progression was longer upon presence of a local recurrence. A higher proportion of patients responded to treatment with irinotecan than to treatment with capecitabine. The highest number of patients responded to treatment of liver metastases. In the analysis of the distribution of local recurrences following the second line of treatment, no significant difference was detected between the responding group and the group with progression ($p = 0.0761$). In the logistic regression, local relapse, next to performance status, proved to represent an independent variable affecting the response to treatment. Apart from the group of patients with local recurrence and liver metastases, the remaining groups of patients manifested low numerical force.

In the group of patients treated with irinotecan, the grade of histological malignancy G was estimated in 64/82 patients and in patients treated with capecitabine in 50/82 patients (in the total of 114/164 patients). The distribution of grades was as follows: G1 in 16/112 patients (1 local relapse), G2 in 2/112 patients (25 local relapses), G3 in 6/112 patients. In 45 patients following radical surgery the estimated distribution was as follows: Indeterminate G in 16/ 45 patients, G1 in 3/45 patients, G2 in 26/45 patients. The effect of the grade (G) on the duration of time to disease progression was evaluated in 45 patients primarily operated with radical intention (irinotecan and capecitabine). In 16/45 patients the grade of histological malignancy was not evaluated, in the remaining 29 patients the presence of G3 was not detected, including 6 out of 45 patients in either of the groups, manifesting local reccurence. Statistically, the

grade of histological malignancy could not be demonstrated to affect the response to treatment.

In the both groups together, a positive response to the treatment (WHO 1–3) was demonstrated in a total of 34 patients. In the irinotecan group, attainment of WHO 3 response (15 patients) required administration of the mean of 6.8 cycles of chemotherapy (range of 2 to 11 cycles), attainment of WHO 1 response (3 patients) required the administration of the mean of 5.33 cycles of chemotherapy (range of 4 to 9 cycles). In the group treated with capecitabine attainment of WHO 3 response (15 patients) required the mean of 6.37 cycles of chemotherapy (the range of 4 to 10 cycles), attainment of WHO 2 response (1 patient) was obtained after 6 courses of chemotherapy. In 130 patients progression of the disease developed in the course of second line chemotherapy, after the mean of 5.5 months. In the group of irinotecan the time period till progression amounted to 5.1 months, following the mean of 6 cycles (the range of 1 to 18 cycles). In the group of capecitabine the time till progression amounted to 5.7 months, following the mean of 5.3 cycles (the range of 2 to 11 cycles). In the patients with no response to the treatment, the time till progression of the disease was significantly shorter ($p = 0.0001$).

In the evaluation of the concomitant diseases prior to treatment, dysfunction of kidneys, liver and cardiovascular, endocrine and haemopoetic system were taken into account. The evaluated variables included blood morphology, serum concentrations of bilirubin, glucose, transaminases, creatinine and urea. Viral infections were not analyzed in the patients. Prior to the treatment, pathology in liver function was detected in 24/164 patients and metastatic lesions in 90/164 (including 14 out of 24 with the earlier detected dysfunction). Statistically, no effect of chronic diseases of kidneys, liver, presence of other tumors, diabetes mellitus or diseases of cardiovascular system (including differences in distribution of bilirubin, creatinine, glucose) could be demonstrated as a response to second line chemotherapy.

In over 20% of the patients following treatment with irinotecan and in 28% of the patients following treatment with capecitabine, the courses of chemotherapy were followed by lymphopoenia of 3rd or 4th grade. The distribution of lymphocyte numbers during the treatment manifested no significant differences ($p = 0.703$) between the group with response to treatment and the group with no treatment.

The conducted analysis, which compared the group treated with irinotecan with the group treated with capecitabine, demonstrated a significant difference in the distribution of leukocyte numbers in the course of treatment ($p = 0.0205$). No significant differences were noted in the distribution of granulocyte numbers in the course of treatment ($p = 0.0897$).

No significant differences were noted between response to treatment and haemoglobin concentration or number of blood platelets before and during treatment.

Statistical analysis failed to detect any relation between side effects of chemotherapy and treatment response to second line chemotherapy.

A complete observation of CEA concentrations was executed in 67 out of all 164 patients. Statistical analysis detected no significant differences with respect to that variable in response to treatment in either of the treatment groups (irinotecan and capecitabine).

Discussion

The absence of significant differences in the analysis of chemotherapy type distribution between patients with response to treatment and patients manifesting progression pointed to the similar value of the two therapeutic regimens. Even if the prognosis for patients who did not respond to 5-FU treatment is poor, the application of the second course of 5-FU in other schemes provides a chance for a response in up to 24% of the cases [1, 2]. Treatment of colorectal carcinoma at its generalized stage aims at alleviating complaints, improving quality of life and prolonging survival. The principal method of treatment involves chemotherapy [3, 4]. The time to disease progression determines the stability of the obtained positive effect of treatment.

In the presented study, the time to disease progression following the second line of treatment was about 6 months, but only around 20% of the patients have responded to the treatment.

Following treatment with capecitabine, the time to disease progression has been slightly longer than in the group treated with irinotecan. In line with some reports, the time to progression following the first line treatment with capecitabine amounted to 4.3 to 5.2 months and, following the second line of treatment with irinotecan, it reached 2.9 to 4.2 months [1].

The statistically significant confirmation of the prevalence of patients with WHO performance score 0 and 1 among responders to the treatment than in the group of non-responders (among whom patients with performance score of 3 and 4 have been more numerous) may be linked to the fact that the low performance score of patients correlates with the reduction of doses, abbreviation of

the therapy period, which resulted in worse treatment effects.

Relevant references recommend that systemic palliative treatment of the second line should be undertaken in patients in good general condition [5, 6]. Treatment of advanced stages of the disease reduces its efficacy in patients. Accurate observation of palliative chemotherapy allows for the identification of patients who have gained a real advantage from such a treatment [2]. The lack of a positive response to the treatment suggests its interruption or modification. Such management is particularly important in regards to borderline indications for operation of metastases [5, 6].

Since the statistical analysis has failed to document a relationship between primary tumor location and the effects of the second line chemotherapy, at present no justification exists for the differentiation of the second line treatment depending on primary tumor location. A marked proportion of reports pointed to the irrelevance of the parameter. However, in cases of relapse, the course of the disease may vary: Rectal carcinoma more frequently induces local recurrences, while colon carcinoma yields distant metastases [7]. No consistent opinion is also available as to the significance of tumor localization in the rectum for an unfavorable prognosis, although at present the opinion prevails that the parameter does not affect the results of treatment [8].

According to certain opinions, securing adequate radial margins upon the resection of the rectum is more difficult in men [8–10].

In the evaluation of operative procedures with radical intention, a prolonged time to progression after the second line of treatment (irinotecan, capecitabine) has been noted after a relapse following primary radical surgery. However, this could not have been confirmed by statistical analysis (the result is near borderline of significance). According to references, the operative approach remains to be the basic method of treatment, while technique and quality of the surgical operation in an advanced disease significantly determine the prognosis [11]. Differences in the operative technique are represented in the results of treatment [12]. Differences in resectability of colorectal carcinoma ranged between 40% and 76% (the mean being 52%), while postoperative mortality ranged from 8% and 30% (the mean being 16%) [3]. The studies proved that better results were obtained in high volume surgical centers (this pertained also to longer survival) [13–15]. It is estimated that 40–50% of patients with colorectal carcinoma following the radical surgery develop distant metastases [16, 17]. An effective palliative chemotherapy may result in the resectability of metastases [18].

An examination of the statistical relationship between the primary stage of the disease and the time to disease progression in the group of patients treated with capecitabine ($p = 0.0258$) proved valuable. In respective references, a significantly higher prognostic correlation with higher stages of advancement in the disease was documented [12]. The stage of the disease proved to be the most important prognostic variable [8].

In the analysis of the extent of lymphatic resection, it remains equivocal if the removal of at least 12 lymph nodes (recommended) in radical surgeries of 44 patients would have prevented the relapse of the disease. Respective literature documented a statistically significant importance of removing the metastatically involved lymph nodes. The presence of such metastases remains to be one of the most important variables affecting the prognosis [17–19]. The principal condition for evaluation involves the removal of the appropriate number of lymph nodes during the surgical procedure and their description by pathologist [9, 20]. For the purpose of an appropriate determination of pN0 trait, the number of excised lymph nodes should include the minimum of 12, since any lower number cannot reliably exclude their involvement by the tumor [7, 20]. The probability of detecting metastases in the lymph nodes increases in accordance with their number examined. [8, 21]. This is not justified in the cases of applying radiotherapy before surgery.

The statistical analysis has shown that age was not a variable linked to the relapse of the disease. According to the references, older patients may experience a similar benefit (response, time to progression) to the applied chemotherapy as do younger patients. According to the respective references, age belongs to variables carrying no unequivocally proven prognostic significance [22, 23]. However, reports on the matter vary [1, 7].

As demonstrated in the statistical analysis, the elongation of survival to progression in women treated with capecitabine (in total of 164 patients) has pointed to better effects of treatment in the group. In the analyzed references, sex belonged to variables of no unequivocally proven prognostic significance [22]. Logistic regression has shown that local relapse represented an independent variable affecting the response to treatment.

The available literature contains the claim that local recurrence in the pelvis minor following a non-radical operation represents a distinct problem [24, 25]. The tumor location, which poses technical difficulties during primary surgery, seldom allows for surgical treatment in the case of recurrence, but it might remain within reach of

palliative radio- and chemotherapy. The rectum represents a more frequent primary location of the recurrent tumor [25].

Indirectly, one may conclude that G3 trait has not been among the principal factors linked to relapse in the evaluated cases. Nevertheless, an observation of a larger group of patients is necessary. According to reports, the histological malignancy grade G represents a variable additionally affecting the prognosis [22]. A certain subjective character of pathological evaluation and tumor heterogeneity should also be taken into account. It seems significant also to take into account the maturity of the tumor in the context of the stage of advancement manifested by the disease [7].

Observations of the patients have been conducted with the intention to evaluate the time to disease progression in individual types of responses. However, since the prevailing type of response involved stabilization of the disease (partial and total remission involving individual cases only), such a comparison could not be conducted.

Statistical analysis has demonstrated that in patients who did not respond to the second line treatment, the time to progression was significantly shorter than in responders. It should be taken into account that in certain situations diagnosed as a progression we may be in fact dealing with a slowed down proliferative process due to the effects of chemotherapy and the progress of untreated disease would be much more rapid.

The fact that statistical analysis has failed to demonstrate the effects of chronic hepatic diseases, other tumors, cardiovascular diseases, capacity of bone marrow, chronic renal diseases, diabetes mellitus on the response to treatment in either of the treated groups may be explained by the fact that patients with excessively pronounced pathologies were disqualified from treatment.

Statistical analysis has demonstrated a significant difference in distribution of leukocyte numbers in the course of treatment, probably linked to the side effects of the very treatment.

In studies on 603 patients with colon carcinoma and a significant presence of lymphocytes T in the removed tumor, their number was found to allow a prediction of the result of treatment more accurately than would have been possible with the stage of the disease or condition of lymph nodes [26]. Tumors less inflamed by lymphocytes were suspected to bear a worse prognosis [27]. Some of the reports drew attention to the predictive significance of density manifested by CD3 lymphocytes (TIL) in the invasive margin of a deeply infiltrating (pT3-T4) carcinoma, but respective reports on the subject are not unequivocal [27].

Since the conducted analysis has failed to demonstrate statistically significant differences in the distribution of manifestation of evaluated side effects developing as a result of the two regimens of chemotherapy, the complications probably exerted no decisive influence on the final effect of treatment. In relevant references the most frequent signs in the case of irinotecan involved acute and chronic diarrhea syndromes of a cholinergic background, conditions of deep neutropoenia and thrombotic-embolic syndromes, in the case of capecitabine the most frequent were dermal syndromes, particularly the "hand and foot" syndrome [27, 28]. Our own observations were confirmed by the data found in the literature on the subject.

Since the conducted statistical analysis has disclosed no significant differences in CEA levels before treatment between patients who responded to second line chemotherapy and those who did not respond to it, it should be accepted that the parameter was not linked to the response to treatment in any or the examined schemes. However, a complete observation of CEA concentrations has been conducted in only 67 out of all 164 patients. Some reports inform that CEA level depends on factors which carry no unequivocally proven prognostic significance while other find a statistically significant effect of preoperative CEA levels on distant results of treatment [22, 29, 30].

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