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Review Article

PALLIATIVE TREATMENT OF GASTRIC ADENOCARCINOMA

Tratamento paliativo do adenocarcinoma gástrico

Fernando de Oliveira **SOUZA**, Luis Carlos Moreira **ANTUNES**, Luis Humberto Ribas dos **SANTOS**

From Departamento de Cirurgia e Serviço de Oncologia e Radioterapia do Hospital Universitário da Universidade Federal de Santa Maria, Santa Maria, RS, Brasil.

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Correspondência:
Fernando de Oliveira Souza,
e-mail: fsouza@via-rs.net

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ABSTRACT – *Introduction –* Although decreasing in the well developed countries, gastric adenocarcinoma still represents the third most common cancer in males worldwide. Its mortality is very high because of the lateness of its diagnosis over advanced lesions, which turns palliative its treatment in the majority of the cases. ***Method –*** Literature review using CAPES, PubMed and Bireme sites as well as the abstracts of the 8 º International Gastric Cancer Congress which was held in Krakow in 2009. ***Conclusions –*** The release of new anticancer drugs against gastric cancer is providing a revival of gastrectomy as an effective palliative treatment of advanced gastric cancer. New protocols are being published, showing better results in the treatment of this disease.

RESUMO – *Introdução*: Embora decrescendo nos países do chamado primeiro mundo, o adenocarcinoma gástrico mantém-se como terceiro tumor mais frequente no sexo masculino mundialmente. Sua mortalidade é muito elevada, fruto do diagnóstico tardio em lesões muito avançadas, o que frequentemente torna paliativo seu tratamento, motivos pelos quais se justificam estudos no sentido de melhorar estes resultados. ***Método*** – Revisão da literatura através do portal de periódicos da CAPES indicados por busca no sites da Bireme e PubMed. Além disso, foram consultados os sumários do 8º Congresso Internacional de Câncer Gástrico em 2009. Foi apresentada uma sugestão de algoritmo de atendimento destes pacientes. ***Conclusões*** – O surgimento de novas drogas anticancer, mais efetivas, está propiciando novas alternativas para a ressecção gástrica como tratamento paliativo. Novos protocolos estão surgindo mostrando boas perspectivas para melhorar os resultados desta doença.

INTRODUCTION

Although decreasing in the so-called first world countries, gastric adenocarcinoma (GA) remains the most frequent in males (ranks third after prostate and lung), but its importance is even greater because of its high mortality (second position after lung cancer). It was computed globally in the year 2008 almost one million new cases and 780,000 deaths[11].

In Brazil, are expected in 2010, approximately 22,000 new cases considering both sexes, according to estimates from the National Cancer Institute[20].

Analyzing the results obtained in the treatment of gastric adenocarcinoma in the Western world, it can be considered it, in general, as palliative, since recurrences are more likely to happen in follo-up and five year survival rate reaches only 20% on average, computing all stages together.

Even zero residual resections (R0) with curative intent as proposed by Hermanek[24] in 1994 - microscopically negative surgical margins and the tumor bed -, recurrence reaches 52%; involvement is most on locoregional lymph nodes or peritoneum. Though, one can already see the need to establish additional criteria for defining operation with curative intent because, as noted, in face of such high rate of disease recurrence. More correct would be to define R0 as "no residual tumor detectable by conventional diagnostic methods." The curative intent should include negative cytology of peritoneal

fluid (5% to 20% of patients undergoing resection have malignant cells in peritoneal cavity even in the absence of macroscopic lesions, especially in T3 tumors [43], and negative test for cells in the peripheral blood, portal (found in 18% to 24% of cases [39]) and bone marrow of patients (within 50% of cases pre-operatively[36]. Karpeh Brennan[12] and consider gastric resection in patients with T3 tumors as palliative for the high incidence of positive cytology for malignant cells in these cases.

This review is focused on palliative treatment of surgical point of view, chemotherapy and their associations, adding proposition of an algorithm (Figure 1) - a proposal that aims to be submitted to the scientific community -, always treating advanced tumors.

METHOD

It was used the keywords "stomach" and "adenocarcinoma" to search PubMed and BIREME and then selected the relevant publications in the CAPES Portal with special attention to metanalysis and randomized controlled trials. Moreover, the Abstract Book was revised from the 8th International Congress of Gastric Cancer held in Krakow, Poland in 2009.

Surgical treatment

From the standpoint of surgical resection, whenever possible, palliative care should be seen as a benefit/risk ratio, understanding how to benefit the quality and quantity of patient survival. For this analysis it has to individualize each case based on the degree of impairment caused by the disease (staging).

The first step in the algorithm to these patients is the assessment of their suitability to receive some treatment, whether surgical, chemotherapy or radiotherapy. For this, besides the routine tests, adoption of performance scales as the Karnofsky[26] or ECOG[30] must be done. Those considered unfit are referred to the best supportive care, suitable for the clinical staging including physical examination looking for disseminated disease, for example, the platform Blumer at digital rectal examination, imaging studies including computerized tomography of the pelvis, abdomen (with contrast) and chest, and blood tumor markers (CEA and CA 19-9). Abdominal tomography should seek evidence of satellite lymph node involvement (lymph nodes greater than 1 cm in diameter) and signs of liver metastases, irresecability eg diffuse invasion of the retroperitoneum with involvement of large vessels. The gastroscopic study with previous biopsy should ideally be accompanied by endoscopic ultrasound.

After this initial evaluation, excluded those with bleeding gastric tumor or obstruction and others (especially those with gastric tumors involving the whole body and/or enlarged lymph nodes>1 cm) are referred to laparoscopy with peritoneal lavage. From these results, patients with diffuse disease (far advanced gastric cancer - FAGC) with a factor of incurability, are referred for resection of gastric tumor reduction followed by adjuvant treatment. Those with incurable multiple factors go into palliative chemoradiation. Patients without evidence of diffuse disease (local advanced gastric cancer - LAGC) are indicated for perioperative chemotherapy with three cycles before and three after surgery. These patients should be monitored in relation to the response to medication using RECIST criteria [19]; in case of no response, should be anticipated his referral to a surgical procedure.

The recommended operation is gastrectomy with D2 lymphadenectomy, respecting the safety margins recommended for diffuse and intestinal tumors and freezing evaluation of para-aortic lymph nodes (group 16). In patients with tumors considered inoperable, pre or peri-operatively, with no diffuse disease with

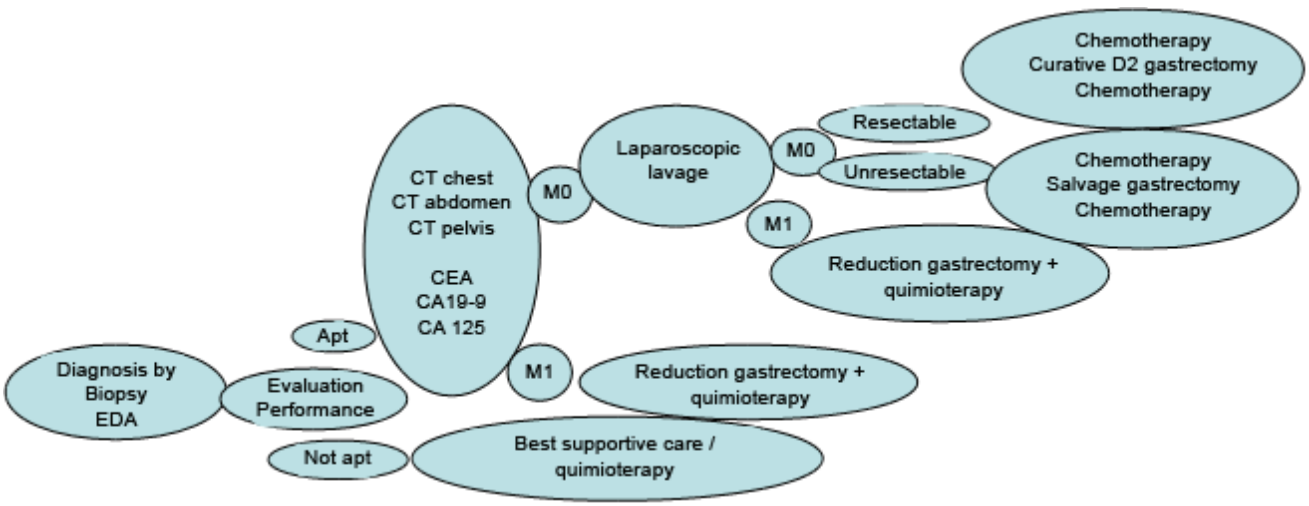

FIGURE 1 – Algorithm proposed to better guide the management of patients with gastric cancer in palliative care

multiple incurable factors, the recommended treatment is neoadjuvant therapy in an attempt to shrink the tumor and followed by operating review (2 nd look) (Figure 1) .

Multivisceral resection is indicated in the absence of diffuse disease or systemically.

All these procedures should be performed in centers with high volume of cases in the treatment of gastric cancer.

Comparing with literature, stand out as the most controversial points of the algorithm - in relation to palliative surgical treatment of the AG - the gastrectomies of tumor reduction (reductive gastrectomy) for adjuvant treatment in patients with one incurable factor, and salvage gastrectomy after neoadjuvant treatment in patients initially considered inoperable.

In the first situation, was activated in February 2008 a randomized controlled trial (RCT) from Japan (JCOG 0705) and Korea (KGC01) comparing two groups of patients with stage IV AG with one incurable factor, either hepatic or peritoneal distant lymph nodes, some patients were conducted to chemotherapeutic treatment alone and the others directed to the tumor reduction gastrectomy followed by chemotherapy regimen with expected 10% increase in survival at two years in the surgical group[38]. Indeed, in 2006, Saidi et al.[34] reported increased survival of 10.4 months in patients operated concluding that there is a role for what they called palliative gastrectomy in patients with stage IV AG.

Regarding to salvage gastrectomy, with the evolution and development of new anticancer drugs, are emerging papers suggesting that in patients with disseminated or unresectable AG, operations resection after neoadjuvant treatment is satisfactory[14,25,44].

Palliative chemotherapy

Metastatic gastric cancer: clinical supportive care vs. combined chemotherapy treatment

In 1977, Glimelius et al.[23] published a randomized study that showed higher survival rates with better quality of life for patients receiving palliative chemotherapy compared with best supportive care (69% vs 47%, p <0.05) . However, at least three studies of the decade have not confirmed these results[18,28,33].

With the evolution of both chemotherapy and supportive care, new studies in the 90´s showed clear benefit in favor of palliative chemotherapy. Metanalysis published by Wagner et al, with three studies including 184 patients showed HR 0.39 (CI: 95%, 0.28 ª 0.52) for overall survival in favor of chemotherapy[41].

Chemotherapy with single agent vs combined regimen

Fluorouracil (5FU) was the most extensively studied agent chemotherapy for metastatic gastric cancer, being used as monotherapy in 10 studies, nine regimens of combination chemotherapy for a total of 11 studies reviewed by Wagner et al. With 1,472 patients comparing chemotherapy with a single agent vs combination, the authors found a HR of 0.83 (CI: 95%, 0.74 to 0.93) for survival in favor of combination regimens, corresponding to gain in median survival of about a month. Six of these studies, which used 5-FU as monotherapy, reported rates of death related to treatment of 1.7% for combined treatment and 0.8% for 5FU as a single agent[41].

Cisplatin and anthracyclines in combination regimens of chemotherapy

The metanalysis of Wagner et al also evaluated three randomized trials involving 501 patients comparing combination cisplatina/5FU with or without anthracyclines, demonstrating statistically significant benefit in favor of the scheme with three drugs (HR = 0.77, 95% CI, 0, 62 -0.91), overall survival with a gain of about two months. This review also assessed the role of cisplatin in combination with three drugs, with seven studies comparing 5-FU/anthracycline/cisplatin vs 5-FU/anthracycline, checking gain an overall survival of approximately one month (HR 0.83, 95% CI, 0, 76-.91)[41].

The regimen ECF (epirubicin, cisplatin and 5FU in continuous infusion) was compared with PELF, a combination of four drugs (epirubicin, cisplatin, leucovorin and 5FU bolus) that resulted in the death rate related to treatment of 3.3% vs 0,6% (OR=5.36 95% CI, 1.1 to 27.4, p=0.028), suggesting increased toxicity for PELF. Two other studies looked at quality of life, demonstrating superiority of ECF over the 5FU/doxorrubicina/metotrexate and mitomicina/ cisplatina/5FU.

Oxaliplatin and capecitabine in combination regimens of chemotherapy

Cunningham et al. presented the data of a phase III study (REAL-2) with 1002 patients randomized into four arms in 2X2 format, with the ECF as the reference arm, and evaluating non-inferiority of the substitution of capecitabine for 5FU and cisplatin by oxaliplatin. The capecitabine was not inferior to 5FU (HR 0.86, CI: 95%, from 0.80 to 0.99) and oxaliplatin was not inferior to cisplatin (HR 0.92, CI 95% 0.80 - 1.10). The group that received the EOX regimen (epirubicin/oxaliplatin/ capecitabine) showed higher survival at one year (46.8% vs 37.7%, p=0.02) and overall survival (11.2 vs 9.9 months, p = 0.02) when compared to ECF. The four schemes had similar response rates, with no statistically significant difference with 47.9% for EOX, 46.4% for EOF (epirubicin, oxaliplatin and 5FU), 42.4% for ECX (epirubicin, cisplatin and capecitabine) and 40 7% for ECF. The oxaliplatin-containing regimens were well tolerated, with a lower incidence of severe neutropenia, alopecia and nephrotoxicity, but with higher rates of peripheral neuropathy and diarrhea[16].

Another phase III study with 220 patients compared a regimen containing oxaliplatin (FLO: oxaliplatin/5FU/

leucovorin) vs regimen of cisplatin (FLP: cisplatina/5FU/leucovorin) in relation to progression-free survival (PFS) based on intention to treat analysis. Was found a trend toward TLP for the FLO scheme, although not statistically significant (5.8 versus 3.9 months, p=0.077), as well as for overall survival (10.7 vs 8.8 months). However, when analyzed over 65 years (n=94), the FLO regimen was significantly superior to the response rate (41.3 vs 16.7%, p=0.012), time to treatment failure (5.4 vs 2.3 months, p<0.001) and PFS (6.0 vs 3.1 months, p=0.029), and an increase in overall survival (13.9 vs 7.2 months). This group also showed lower toxicity as the grades 1-4 leukopenia, nausea, fatigue and nephrotoxicity, but higher incidence of peripheral neuropathy[7].

Docetaxel

The use of docetaxel in first line advanced gastric cancer was investigated in the study TAX 325, whose schemes phase II compared docetaxel/cisplatin (DC) and docetaxel/cisplatina/5FU (DCF) in order to identify the most effective regime. The DCF was superior in efficacy (43% vs 26%) and time to progression (5.9 vs. 5 months), being chosen for phase III. For this phase, 457 patients were randomized into two groups to receive the first line of DCF or CF (cisplatin and 5FU). Again, the DCF was superior, with better results over time to progression (5.6 vs 3.7 months, p=0.0004), overall survival (9.2 vs 8.6 months, p=0.02), two-year survival (18% vs 9%), overall response rate (37% vs 25%, p=0.01) and analysis of quality of life. However, the toxicity was significantly higher, with rates of grade III and IV neutropenia 82.3%, and incidence of febrile neutropenia from 30% in the DCF; it must monitor carefully adverse reactions of this scheme[4,5,40].

I rinotecano

The V-306 study evaluated the use of irinotecan in combination regimens for first line advanced gastric cancer in a phase II study initially comparing IC (irinotecan and cisplatin) and ILF (irinotecan, fluorouracil and leucovorin), defining the superiority of the latter[13]. The phase III study of the V-306, compared ILF with CF, and showed a trend towards longer time to progression (5 vs 4.2 months, p=0.088) and response rate (31.8% vs 25.8%) for the IFL, but not statistically significant. With a similar mean survival time in both groups (9 vs 8.7 months, p=0.53), but lower toxicity with IFL group, this can be used as an alternative to the regime CF[17]. Bouche et al.[10] Published a phase II study comparing irinotecan with another scheme, combined with leucovorin, 5FU bolus and 5FU in continuous infusion (FOLFIRI) with LF (5FU and leucovorin) or CLF (cisplatin, 5FU and leucovorin). The objective response rates, TP and SG were higher with the regimen FOLFIRI

S-1

The use of a fourth generation of fluoropyrimidines, called S-1, and composed of tegafur/gimeracil/oteracil has been investigated mainly in Japan, where it was approved as adjuvant or palliative chemotherapy for patients undergoing curative resection. Other Asian countries also have established systems with S-1 as adjuvant (Korea) or as standard treatment in advanced gastric cancer (Korea, Singapore and China). The SPIRITS, a phase III study conducted by Koizumi et al.[29] with 305 patients, compared with S-1 alone S-1/cisplatina, finding the superiority of the combination regimen compared with overall survival (p=0.04, HR=0.77, CI 95% 0.61-0, 1998) and response rate (54% vs 31%). Despite the higher toxicity (increased incidence of neutropenia, anemia, nausea and anorexia) of the combined regimen, this was generally well tolerated[29]. Another phase III Japanese study, published by Boku et al., Showed similar overall survival for the S-1 when compared to 5FU or combination irinotecan/cisplatin (median survival times of 11.4 vs. 10.8 vs. 12.3 months)[9].

As the rate of metabolic conversion of the prodrug, oral tegafur for fluorouracil appears to be different depending on the ethnic population, was conducted a phase I study to establish the maximum tolerated dose of S-1/cisplatina in the West[3]. After assessing the efficacy and safety of this combination in a phase II multicenter study, Ajani et al. published the results of the study FLAGS which included 24 countries and 146 centers with 1053 patients stratified (center, number of metastatic sites, prior adjuvant chemotherapy and extent of disease) and randomized to receive or S-1/cisplatina 5FU/cisplatina (5FU in 24h infusion). The scheme S-1/cisplatina showed no statistically significant increase in overall survival (8.6 vs 7.9 months, with HR: 0.92, 95% CI, 0.80 to 1.05, p=0.20) but resulted in less toxicity with lower rates of neutropenia grade 3/4 (32.3% vs 63.6%), complicated neutropenia (5% vs 14.4%), stomatitis (1.3% vs 13.6%), hypokalemia (3.6% vs 10.8%) and treatment-related death (2.5% vs 4.9%, p<0.05)[6].

Monoclonal antibody

It was approved in Europe the use of trastuzumab combined with chemotherapy for first line treatment in advanced gastric tumors positive for HER2[37]. Trastuzumab is a monoclonal anti-body that blocks the HER2 receptor, involved in cell growth. A phase III multicenter, multinational, randomized (ToGA) found a reduction in mortality of 26% for patients receiving the drug combined with chemotherapy (5FU or capecitabine in combination with cisplatin) compared to chemotherapy alone. The median overall survival was 13.8 months found in the trastuzumab group versus 11.1 months in the control group, making this the first monoclonal anti-body to show survival benefit among several other targeted therapies that are being tested for gastric cancer[31].

Locally advanced gastric cancer

The definition of locally advanced gastric cancer has different interpretations depending on the author and the institution. Can be regarded as the primary tumor that surgeons do not expect microscopically resected with negative margins (no possibility of curative resection as surgical exploration or preoperative evaluation with computed tomography, endoscopic ultrasound, laparoscopy, or other imaging tests, local recurrence without evidence metastases). Or, you can include completely resectable disease, but with high risk factors for local recurrence or distant metastases (nodal involvement, extension beyond the gastric wall, or both)[1].

Patients with deep invasion, bulky and locally unresectable due to infiltration of adjacent structures, they received only palliative chemotherapy. However, with the introduction of perioperative chemotherapy this scenario has been modified. The neoadjuvant chemotherapy can reduce tumor volume, the patient is operable, to avoid delay in treatment of possible micro-metastases, to improve the tolerability of chemotherapy, as adjuvant chemotherapy may have a higher toxicity due to high energy consumption and possible post-operative complications, and also test the patient's response to a given drug, defining the rules used in the postoperative period[45].

Schumacher et al. published in 2001 the results of five years of follow-up of a phase II study with 42 patients with locally advanced gastric cancer (stages IIIA, IIIB and IV). These were initially evaluated with endoscopy, endoscopic ultrasound, CT scan to rule out infiltration of adjacent organs and detection of distant metastasis, and laparoscopy to exclude occult peritoneal carcinomatosis. Each patient received three or four cycles of combination chemotherapy (doxorubicin/cisplatin/etoposide). After re-evaluation, 36 patients underwent total gastrectomy, obtaining pathological complete resection in 31 (73.8%). The overall median survival of 42 patients was 19.1 months, and those who did not receive surgical treatment, survival was only 1.5 months vs. 22.2 months for those treated surgically (7.6 months with incomplete resection vs 28.4 months for complete resection, p=0.0001). It is noteworthy higher survival rate associated with higher clinical response to chemotherapy, the median survival of 45 months [35]. Several other studies have shown benefit for neoadjuvant chemotherapy in locally advanced gastric cancer, with increased resectability (42.4%) and survival[2,21,22,27,32,42,44].

In 2006, Cunningham et al. published the results of the MAGIC study, where 503 patients were randomized operable in a phase III study to receive three cycles of ECF before and after surgery or surgery only. Patients in the group of peri-operative chemotherapy had higher rates of T1 and T2 (51.7% vs 36.8%) on post-operative pathologic analysis, and a gain of 13% in the five-year survival (36% vs 23 %), and have no statistically significant differences in surgical morbidity between the two groups (45.7% vs 45.3%). There was a higher number of curative operations (79.3% vs 70.3%, p=0.003), increased progression free survival (HR=0.66, 95% CI 0.53 to 0.81) and survival overall (HR=0.75, 95% CI 0.60 to 0.93) in the chemotherapy arm with[15].

While in metastatic disease the doses of chemotherapy regimens should not be so high - while avoiding toxicities relevant with the intention of improving the quality of life with greater survival - on the other hand in locally advanced disease neoadjuvant chemotherapy aims to increase rates resection and possible cure, and should be used in combination regimens with two or three drug doses and less flexible.

CONCLUSION

The emergence of new anticancer drugs, more effective, is providing new alternatives to gastric resection as a palliative treatment. New protocols are emerging showing good prospects for improving outcomes of this disease.

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