World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i27.8993

World J Gastroenterol 2014 July 21; 20(27): 8993-8997
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

De-escalating therapy in gastric aggressive lymphoma

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Received: November 29, 2014 Revised: January 14, 2014
Accepted: March 12, 2014
Published online: July 21, 2014

Abstract

The treatment of primary gastric diffuse large B-cell lymphoma (DLBCL) has changed radically over the last 10–15 years, with the abandonment of routine gastrectomy in favor of more conservative therapies. Low-level evidence suggests that consolidation radiotherapy could be avoided in patients with limited-stage DLBCL of the stomach who achieve complete remission after rituximab-CHOP combination. Small, recent prospective trials suggest that selected patients with limited-stage *Helicobacter pylori* (*H. pylori*)-positive DLBCL of the stomach and favorable prognostic factors can be managed with antibiotics alone, with excellent disease control and cure rates, keeping chemo-radiotherapy for unresponsive patients. This recommendation should equally regard patients with mucosa-associated lymphoid tissue-related or *de novo* DLBCL. Future studies should be focused on the establishment of reliable variables able to distinguish the best candidates for exclusive treatment with *H. pylori* eradication from those who need for conventional chemo-immunotherapy.

Key words: Diffuse large B-cell lymphoma; Gastric lymphoma; *Helicobacter pylori*; Antibiotic therapy; Rituximab

Core tip: Therapeutic intensity has been progressively reduced in patients with limited-stage diffuse large B-cell lymphoma of the stomach, with a consequent improvement in tolerability and quality of life, and with unimpaired survival figures. In particular, patients with *Helicobacter pylori* (*H. pylori*)-positive lymphoma and favourable prognostic factors can be managed with antibiotics alone, with excellent disease control and cure rates, keeping chemo-radiotherapy for unresponsive patients. Future studies should be focused on the establishment of reliable variables able to distinguish the best candidates for exclusive treatment with *H. pylori* eradication from those who need for conventional therapy.

Cuccurullo R, Govi S, Ferreri AJM. De-escalating therapy in gastric aggressive lymphoma. *World J Gastroenterol* 2014; 20(27): 8993-8997 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i27/8993.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i27.8993

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma category arising in the stomach, representing 5% of all gastric malignancies. DLBCL usually arises as a primary form, which is a tumor limited to the gastric wall, with or without involvement of perigastric lymph nodes (stage IE-IIE). The treatment of primary gastric DLBCL (PG-DLBCL) has greatly evolved in the last decades, mostly due to the development of new chemoimmunotherapy combinations, progress in radiation technology, improvement of sensitivity of procedures used in staging and response assessment and expansion of etiopathogenic knowledge. In particular, gastrectomy-based strategies have been abandoned, the role of radiation therapy has been downsized, whereas indications of

chemoimmunotherapy and antibiotic therapy have been extended, resulting in important organ-salvage benefits and iatrogenic toxicity reduction without survival impairment. However, the level of evidence supporting therapeutic choices is still low since available literature is mostly constituted by retrospective analyses of small and heterogeneous series, whereas only a few prospective trials with completed accrual are available. This review travels through the changes in the therapeutic management of patients with PG-DLBCL introduced in the last decade, defines the impact of each treatment component and critically analyzes the supporting evidence.

FROM GASTRECTOMY TO CONSERVATIVE CHEMO-RADIOTHERAPY

For several years, surgery played a central role in diagnosis, staging and treatment of PG-DLBCL. Its goal in these tumors has gradually changed from curative to staging and palliation, with less concern for radicality. Gastrectomy, once considered essential to diagnose gastric lymphomas, today has been replaced by modern endoscopy procedures through which multiple biopsies of gastric mucosa allow an accurate histopathological diagnosis. Also computer tomography-scan and ^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) are important to establish the disease's anatomical extension as this is a crucial prognostic factor, reducing the role of surgery as staging procedure.

Large retrospective studies published more than 15 years ago have suggested that patients with PG-DLBCL could be managed with an organ-sparing strategy based on a combination of anthracycline-based polychemotherapy and consolidative irradiation of the stomach and perigastric lymph-nodes[1]. These studies have suggested that the extent of surgery (excision or biopsy) has no impact on outcome of PG-DLBCL and that patients' quality of life after conservative nonsurgical treatment is remarkably better than after gastrectomy, with a reduced risk of severe malabsorption syndrome, vitamin deficits, anemia, dumping syndrome, secondary nutritional depletion and infections among others.

These preliminary observations have been confirmed by a large controlled clinical trial, where 589 patients with newly diagnosed PG-DLBCL have been randomly allocated among gastrectomy alone, gastrectomy plus radiotherapy, gastrectomy plus chemotherapy, and chemotherapy alone, with a 10-year overall survival (OS) of 54%, 53%, 91%, and 96% ($P < 0.001$), respectively[2]. Late toxicity has been more frequent and severe in patients who undergoing gastrectomy, with more cases of lethal complications. Lymphoma progression has been significantly less common among patients treated with chemotherapy, with rare cases of perforation, obstruction and hemorrhage in patients managed with chemotherapy alone. Accordingly, this trial has demonstrated that patients with PG-DLBCL must be managed with anthracycline-based chemotherapy, and that the addition of primary gastrectomy results in impaired survival figures due to significantly higher complications rates[2].

These results are in line with a retrospective comparison of two small prospective trials performed between 1988 and 1996[3]. The first one has been a Groupe d' étudé des Lymphomes Digestifs (GELD) trial addressing primary gastrectomy followed by chemotherapy in 48 patients with PG-DLBCL; the second one has been a Groupe d'étudé des Lymphomes de l'Adulte trial addressing anthracycline-based chemotherapy as exclusive treatment. Patient characteristics distribution has been similar between two series, with the exception of higher rates of increased serum lactate dehydrogenase levels and large tumors in GELD series. Comparison has been limited to patients with International Prognostic Index of 0-1. After a median follow-up of 59 mo (range 3-128), the 5-year OS has been 91% for both subgroups, suggesting that gastrectomy is superfluous in patients with low-risk PG-DLBCL[3]. Thereafter, the role of gastrectomy as part of first-line treatment of PG-DLBCL has progressively declined. Presently, surgical approach remains confined to resolution of chemotherapy-related complications, like bleeding or perforation, which affect < 1% of PG-DLBCL patients managed with upfront chemotherapy[2].

FROM CONSERVATIVE CHEMORADIOTHERAPY TO CHEMO (IMMUNO) THERAPY ALONE

Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody that has drastically changed the natural history and therapeutic approaches to DLBCL patients[4]. In the pre-rituximab era, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy followed by involved-field radiotherapy (IF-RT) was the standard of care for limited-stage DLBCL and, consequently, for patients with PG-DLBCL[5]. However, large randomized trials failed to demonstrate a survival benefit with the addition of IF-RT after anthracycline-based polychemotherapy in DLBCL patients (reviewed in[4]), and the major concerns of secondary radio-induced malignancies and quality-of-life impairment in patients with a high cure rate led physicians to avoid consolidative radiotherapy in these patients, even in PG-DLBCL. In a small, pre-rituximab comparative trial[6], patients with PG-DLBCL who achieved a complete remission after four courses of anthracycline-based chemotherapy were randomly allocated between other two chemotherapy courses or IF-RT 30 Gy. The addition of IF-RT did not increase iatrogenic toxicity, but did not modify survival figures, with a 5-year OS of 82% for both arms. However, induction chemotherapy was heterogeneous and the trial was undersized for comparison since it was prematurely closed, with a consequent small number of patient accrued and scarce events.

In the rituximab era, the role of consolidation radio-

therapy as part of first-line treatment in patients with limited-stage DLBCL is still matter of debate. A worldwide use of rituximab is associated with a better quality of response, and a concomitant development of metabolic tools, like ^{18}FDG-PET, allowed a better definition of extension of disease and therapeutic response. Randomized trials assessing the role on consolidation IF-RT in DLBCL patients do not exist in the rituximab era, but large retrospective studies seem to suggest that IF-RT is unnecessary in DLBCL patients in complete remission after rituximab-CHOP (R-CHOP chemoimmunotherapy)[4]. In a retrospective Japanese study focused on PG-DLBCL[7], 23 patients have been treated with six courses of R-CHOP and 35 have been managed with 3-4 courses of R-CHOP plus radiotherapy, with a 3-year OS of 91% and 95% (P = 0.27), respectively. With all the limitations of a retrospective study, these results support the use of six cycles of R-CHOP without IF-RT as first-choice treatment option for PG-DLBCL patients[7]. Presently, the effect of radiation therapy on both carcinogenesis and quality-of-life impairment remains matter of debate. In fact, second cancers seem to be related to underlying susceptibility rather than radiation consequence[8], and the use of techniques of highly conformal irradiation is associated with improved tolerability. Nevertheless, available literature seems to suggest that consolidative radiotherapy is unnecessary in patients with newly diagnosed PG-DLBCL in complete remission after R-CHOP therapy.

FROM CHEMOIMMUNOTHERAPY TO *HELICOBACTER PYLORI*-ERADICATING ANTIBIOTIC THERAPY

Half of PG-DLBCL is associated with concomitant areas of mucosa-associated lymphoid tissue (MALT) lymphoma[9-11]. MALT lymphomas constitute an heterogeneous group of indolent malignancies usually arising from sites of infection, chronic irritation and inflammation, where tumor microenvironment, mostly orchestrated by inflammatory cells, is an unavoidable player in the neoplastic process[12]. In the stomach, *Helicobacter pylori* (*H. pylori*), a member of the superfamily VI of Gram-negative bacilli, now called Epsilonproteobacteria, classified as type I carcinogen by the International Agency of Research against Cancer, plays a central role in chronic inflammation, immune system inhibition and related lymphomagenesis[13]. In collaboration with host factors, some *H. pylori* colonization/virulence factors contribute to carcinogenesis, which is favoured by the concomitance of particular genotypes of both pathogen and host. *H. pylori*-related gastric MALT lymphomagenesis is a multi-step process initiated by infection and followed by chronic gastritis, MALT acquisition and, eventually, lymphoma development[14]. Under the antigenic stimulation of *H. pylori*, and thanks to the influence of products from some genetic abnormalities, autoreactive B lymphocytes evolve to an antigen-dependent MALT lymphoma. Some other genetic abnormalities like t(1:14), bcl-10 mutation and trisomies 3, 12 and 18 as well as the effect of DNA-damaging reactive oxygen species produced by neutrophils favour the loss of antigenic dependence[12]. Eventually, other putative karyotype damages related to t(1:14), p15, *Rb, myc*, as well as to p53 inativation, and p16 deletion result in the development of a DLBCL[13], which is usually considered an *H. pylori*-independent growing aggressive tumour.

The most important hints linking gastric MALT lymphoma to *H. pylori* were provided by the observation that *Hp*-associated gastritis reproduces features of acquired MALT, the high prevalence of *Hp* in gastric lymphoma patients (92%), mostly in endemic regions, and the high lymphoma regression rate observed in patients treated with *H. pylori*-eradicating antibiotic therapy (reviewed in[14]). In fact, *H. pylori* eradication with ample spectrum antibiotics is the standard first-line treatment for patients with limited-stage gastric MALT lymphoma associated with this microorganism[9]. This strategy is associated with a complete remission rate of 60%-70% and a 5-year OS of 93%[10,15]. Based on the frequent association among PG-DLBCL, gastric MALT lymphoma and *H. pylori* infection[11], and following the example of gastric MALT lymphomas, some investigators have treated selected patients with PG-DLBCL with antibiotic therapy alone, reporting sporadic cases of lymphoma regression[16,17] and complete remission rates of 27%-87% in a few, small retrospective case-series[18-20], with a relevant risk of reporting bias. More recently, two prospective trials demonstrated that *H. pylori* eradication is feasible and effective as exclusive treatment in patients with PG-DLBCL[21,22]. The first trial has included 16 Taiwanese patients with stage IE "high-grade transformed MALT lymphomas", obtaining a 62% remission rate and no cases of recurrence among responders at a median follow-up > 5 years[21,23,24]. The second trial, named HG-L1, has been a multicentre phase Ⅱ study addressing feasibility, activity and efficacy of *H. pylori* eradication with clarithromycin, tinidazole or metronidazole and omeprazole, as exclusive treatment for Western patients with newly diagnosed PG-DLBCL without aggressiveness indicators (bleeding ulcers, systemic symptoms, increased serum lactate dehydrogenase levels)[22]. The HG-L1 trial has demonstrated that two-thirds of these patients can be efficiently managed with antibiotics alone, thus, avoiding the use of chemotherapy and radiotherapy, which is of importance considering that these patients are often older than 70 years. In fact, this strategy has been associated with a complete remission rate of 63%, a 5-year OS of 94%, and no deaths due to lymphoma. Importantly, *H. pylori* eradication has been associated with long-term remission both in patients with MALT-related and *de novo* DLBCL[18,20], suggesting that near half of *de novo* DLBCL are actually dependent on antigenic stimulation determined by *H. pylori* infection. Conversely to previous reports suggesting that involvement of perigastric

lymph nodes is a negative predictor of response to antibiotics[18,20], half of patients with small (size < 1.5 cm) perigastric lymph nodes enrolled in the HG-L1 trial has achieved lymphoma regression[22]. In this trial, patients who did not respond to upfront antibiotics have been referred to salvage treatment with R-CHOP combination, achieving long-lasting complete remission in all cases, with a median progression-free survival of 55+ months, and antibiotic refractoriness has not been associated with lower survival rates.

Reliable parameters able to distinguish the best candidates for exclusive treatment with *H. pylori* eradication from those who need for conventional chemo-immunotherapy remain to be defined. A few studies have been performed in this context. The prognostic value of ontogenic classification of PG-DLBCL in germinal-centre B-cell like and non-germinal-centre B-cell like DLBCL has been investigated in the HG-L1 trial, reporting that lymphoma regression after *H. pylori* eradication can be observed in both DLBCL subgroups[22]. Other small studies show that nuclear expression of BCL10 predicts *H. pylori* independence of MALT-related DLBCL of the stomach[25], and that autocrine B cell-activating factor of tumor necrosis factor family (*BAFF*) signal transduction pathways may contribute to *H. pylori*-independent growth of this lymphoma[26]. In fact, *BAFF* overexpression seems to be associated with pAKT expression and nuclear expression of *BCL3*, *BCL10* and NF-kappaB, and is more common among MALT-related DLBCL of the stomach unresponsive to *H. pylori* eradication[26]. The predictive value of these and other molecules on large, prospective series remains matter of investigation.

CONCLUSION

On this background, patients with *H. pylori*-related PG-DLBCL and favourable features are eligible for bacteria eradication as exclusive treatment, keeping conventional chemo-immunotherapy for unresponsive patients. This strategy should be equally proposed to patients with *de novo* and MALT-associated DLBCL, and with germinal-centre B-cell like and non-germinal-centre B-cell like DLBCL. Small perigastric lymphadenopathies are not a major limitation to use this conservative approach, but close and accurate disease monitoring is strongly suggested in these patients. Clinical and molecular studies aimed to identify the best candidates for *H. pylori* eradication as exclusive treatment are strongly encouraged. The establishment of different molecular pathways potentially associated with antigenic independence and tumour aggressiveness as well as the analysis of their prognostic role on large series remain important steps forward a rational conservative treatment of gastric DLBCL.

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P- Reviewers: Li QQ, Zheng XF
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ISSN 1007-9327