Effectiveness and Safety of Subcutaneous Rituximab for Patients With Gastric MALT Lymphoma: A Case–Control Comparison With Intravenous Rituximab

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Abstract

Background: Rituximab is a standard treatment for gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML).

Aim: To compare the effectiveness and safety of subcutaneous and intravenous rituximab in a retrospective case-control study.

Methods: All consecutive patients with GML treated with subcutaneous rituximab between January 2017 and December 2018 were included and compared to three matched control patients (based on Ann Arbor classification, presence of t(11;18) translocation, history of previous treatment and type of current treatment) treated with intravenous rituximab between January 2000 and December 2018. Patients with t(11;18) translocation were treated with rituximab in combination with chlorambucil and the other patients were treated with rituximab alone. Effectiveness was assessed at week 52, and safety was assessed through weeks 0 to 52 and compared using chi-squared test.

Results: Twenty-five patients were included in the subcutaneous rituximab group, and 75 were included in the intravenous rituximab group. There was no difference between the groups in complete remission (78% vs. 76%, p=0.99) or overall response rates (91% vs. 89%, p=0.99) at week 52. Safety profiles were similar in both groups, with a significant decrease in postinduction grade 2 injection-related reactions and outpatient hospital length of stay in the subcutaneous rituximab group**.**

Conclusion: In a small case-control study, we did not find any difference in the effectiveness or safety profiles between subcutaneous rituximab and intravenous rituximab for the treatment of patients with GML. We found a decrease in postinduction grade 2 injection-

related reactions and outpatient hospital length of stay in the subcutaneous rituximab group.

Introduction

Primary gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphoma (GML) is the most frequent site of extranodal marginal-zone B-cell lymphoma[1] [2]. For more than 80% of patients, *Helicobacter pylori* eradication allows complete and sustained remission of localized GML[3]. In patients failing to respond to *Helicobacter pylori* (*H. pylori*) eradication, radiotherapy and immunotherapy and/or chemotherapy are recommended for localized disease based on local expertise and patient profiles, while in the case of a more extensive disease, radiotherapy is not indicated[4]. In our centre, we have a long experience of immunochemotherapy which is preferred over radiotherapy.

Oral alkylating agents, mostly chlorambucil, rituximab and the combination of rituximab and chlorambucil have demonstrated their efficacy in treating MALT lymphoma in a phase III randomized controlled study[5]. In those study and in uncontrolled cohort studies, the superiority of the combination of rituximab and chlorambucil compared to monotherapy was also demonstrated[4] [6]. The t(11;18) (q21;q21) translocation, resulting in *API2 and MALT1* gene fusion, is associated with NF-κB pathway dysregulation and resistance to *H. pylori* eradication and alkylating agents alone with no clear impairment of the efficacy of the combination of rituximab and chlorambucil[7] [8(p1)] [6]. It has been proposed that t(11;18)-positive patients should be treated with combination of rituximab and chlorambucil and t(11.18)-negative patients with rituximab alone[6].

Rituximab is usually administered intravenously at a dose of 375 mg/m² with four weekly infusions during the induction phase followed by four monthly infusions during the maintenance phase [6] [5]. The subcutaneous (SC) administration of rituximab has been recently developed as an alternative to intravenous (IV) rituximab with a time- and cost-saving

deliverance. Since 2017, phase I and III studies have demonstrated noninferior pharmacokinetics, efficacy and safety of SC rituximab compared to IV rituximab in various lymphoid malignancies [9] [10] [11]. No difference was found in efficacy and safety profiles with the exception of predictable local injection reaction in the SC rituximab group. Likewise, it has been suggested that the improved delivery of SC rituximab may benefit to patients and healthcare professionals and could be extended to other B-cell hematological malignancies [12]. However, very few data are currently available concerning the use of SC rituximab in patients with MALT GML[13].

In January 2017, we decided to use the subcutaneous formulation of rituximab in the treatment of patients with GML in order to shorten the administration of rituximab and reduce the incidence of infusion-related reaction (IRR). The aim of our study was to assess effectiveness and safety profiles of SC rituximab compared to those of IV rituximab in a retrospective case-control study.

Patients and methods

Study population

In this retrospective study, we included all patients with GML followed in Henri Mondor University Hospital from January 2000 to December 2018. The diagnosis of GML was performed according to the 2008 WHO classification criteria [14]. Patients were recruited from the department's local database and/or the standardized hospital inpatient diagnostic dataset. Inclusion criteria were confirmed diagnosis of GML and treatment with rituximab alone or in combination with chlorambucil. Between January 2017 and December 2018, all consecutive patients were treated with SC rituximab whereas all consecutive patients were treated with IV rituximab between January 2000 and December 2016. Control patients were patients treated with IV rituximab and cases were patients treated with SC rituximab. The ethics committee (Comité de Protection des Personnes, protocol n° PP 13-043) approved the study protocol and all patients before inclusion signed a consent form before inclusion after individual patient interviews. All authors had access to the study data, and reviewed and approved the final manuscript.

Data collection

Tumors were staged according to the Ann Arbor system as modified by Musshoff [15]. The initial evaluation included blood tests for lactate dehydrogenase (LDH) and β2-microglobulin (expressed according to the upper limit of normal or ULN) and thoracic and abdominal computed tomography (CT) scans. In addition, endoscopic ultrasonography (EUS) was performed according to the method described in a previous study [16]. Some patients were assessed at baseline using ^{18}F-fluorodeoxyglucose positron emission tomography. The

maximum standardized uptake value on the GML site was recorded when available. The presence or absence of perigastric lymph nodes was recorded. The diagnosis of GML was made with the criteria of *Isaacson et al:* the presence of diffuse infiltration of the lamina propria by CD20+CD5- centrocyte-like cells associated with lymphoepithelial lesions and reactive lymphoid follicles [17]. The presence of the t(11;18) translocation was determined by amplification and sequencing of the *API2 – MALT1* fusion transcript as previously described, until 2012 and, thereafter, interphase fluorescent in situ hybridization was used to detect MALT1 chromosomal alterations[18].

Treatments

In the IV rituximab group, patients were treated with four weekly infusions of rituximab at a dose of 375 mg/m² as the induction phase, followed by a maintenance phase of four monthly infusions of rituximab at the same dose [19] [20]. In the SC rituximab group, patients were treated with one infusion of IV rituximab infusion at a dose of 375 mg/m² followed by 3 weekly SC rituximab injections at a dose of 1400 mg as the induction phase, followed by a maintenance phase of four monthly injections of SC rituximab at the same dose. Combination therapy was administered with oral chlorambucil 6 mg/m²/day for 42 days, followed by 6 mg/m²/day for 14 consecutive days/month for 4 cycles with rituximab as described above [21]. Rituximab was given with routine premedications, which included methylprednisolone 40 mg, paracetamol 1 g and hydroxyzine 25 mg for the first infusion and then only paracetamol and hydroxyzine for the other IV infusion and SC injection. Intravenous infusion of rituximab was given with progressive increments in the infusion rate to a maximum of 400 mg/hour according to the manufacturer's guidelines with potential slowering and/or transient discontinuation in the case of infusion-related reaction. An IRR of

at least grade 2, meaning a need for at least transient infusion interruption and asymptomatic treatment (methylprednisolone, paracetamol and hydroxyzine), was recorded. The duration of outpatient hospital length of stay was recorded in all patients from the start of rituximab administration to check-out.

Outcome measures

All patients underwent a standardized follow-up protocol with clinical examination, blood tests, upper gastrointestinal endoscopy and EUS, and thoracic and abdominal CT-scans. The evaluations of response were performed at week 6 (W6) (6 weeks after the first rituximab infusion), at week 25 (W25) (4 weeks after the end of the whole treatment), and at week 52 (W52). To assess the histological response, we used the Groupe d'Etude des Lymphomes de l'Adulte (GELA) histological grading system[22] [22]: complete histological remission (CR) was defined by the absence of lymphoid infiltrate or scattered plasma cells and small lymphoid cells in the lamina propria (LP) without lymphoepithelial lesions (LELs) with a normal or empty LP and/or fibrosis; probable minimal residual disease (pMRD) was defined by the presence of aggregates of lymphoid cells or lymphoid nodules in the LP/muscularis mucosae and/or submucosa without LELs with an empty LP and/or fibrosis; responding residual disease (rRD) was defined by a dense, diffuse or nodular lymphoid infiltrate extending around glands in the LP without LELs or with focal LELs and a focally empty LP and/or fibrosis; and no change (NC) was defined as a dense, diffuse or nodular lymphoid infiltrate with LELs and no stromal changes. Complete remission was defined as the combination of the CR and pMRD scores and overall response as the combination of the CR, pMRD and rRD scores[6]. Safety was assessed by the physician in charge of the patient and was retrospectively assessed from patient records. Patients who received at least one dose of therapy were included in the toxicity analysis using the NCI Common Terminology Criteria

for Adverse Events (CTCAE v3.0)[23]. Severe adverse events were defined as adverse events leading to treatment interruption, hospitalization, persistent disability or damage or death.

Case-control study

Controls were selected within our database for matching with cases (three controls for one case). Case-control matching was based on the Ann Arbor classification as modified by Musshoff (Stages I and II *vs*. stages III and IV), the presence of t(11;18) translocation, the history of treatment with rituximab and/or alkylating agents and the type of current treatment (rituximab alone or rituximab plus chlorambucil).

Statistical analysis

Variables were expressed as means ± standard deviations, or medians (interquartile ranges) in the case of continuous data. Nominal and ordinal variables were compared using the chi-squared test or the Fisher's exact test as appropriate, whereas parametric variables were compared using the Mann-Whitney tests and Wilcoxon's matched-pair signed-rank test as appropriate. All analyses were two-tailed, and p values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS statistical software (SPSS Inc., v23, Chicago, IL, USA).

Results

Study population

A total of 140 patients with GML treated with rituximab alone or in combination with chlorambucil were screened for inclusion. Twenty-five patients were treated with SC rituximab (eight with SC rituximab alone and 17 with a combination of SC rituximab and chlorambucil) and were matched with 75 controls (24 with IV rituximab alone and 51 with IV rituximab and chlorambucil). Patient demographic data, baseline disease characteristics and the history of previous treatment are listed in Table 1. Twenty-five patients failed to respond to *Helicobacter pylori* eradication and were treated immediately after eradication failure with rituximab ± cholrambucil. Sixteen patients were previously treated with chlorambucil in four and rituximab alone in twelve including four patients with primary non-response to chlorambucil alone and twelve relapsed after a median period of 4.2 (1.8-5.2) years, and were treated with a combination of rituximab and chlorambucil. Cases and controls were well balanced, with the exception of a lower body mass index (25.7 ± 3.1 *vs*. 24.6 ± 4.2 kg/m², $p = 0.05$) and a higher lactate dehydrogenase level (0.56 ± 0.15 *vs*. 0.67 ± 0.21 upper limit of normal, $p < 0.001$) in the control group.

Effectiveness of subcutaneous rituximab

All patients completed the whole treatment program. Eighty-four patients completed the W6 endoscopic assessment: 18 (72%) in the SC rituximab group and 66 (88%) in the IV rituximab group. All patients completed the W25 assessment. Ninety-eight patients completed the W52 endoscopic assessment, while two patients were not assessed because of underlying comorbidities and the achievement of complete remission at W25. Outcome measures assessing the effectiveness of rituximab alone or in combination with chlorambucil

are listed in Table 2. There was no statistically significant difference between the two groups in complete remission or overall response rates at weeks 6, 25 and 52.

In the SC rituximab group, 44%, 80% and 78% achieved CR at W6, W25 and W52, respectively, while the OR rates were 72%, 94% and 91% at W6, W25 and W52. In the IV rituximab group, 61%, 68% and 76% achieved CR at W6, W25 and W52, respectively, while the OR rates were 83%, 93% and 89% at W6, W25 and W52.The rates of CR and OR were similar in both groups at W6, W25 and W25.

Safety profile

All patients were included in the safety analysis (Table 3). In total, adverse events were noted in 75 (75%) patients, accounting for 100 adverse events, including six serious adverse events, with no difference between the IV and the SC rituximab groups. A total of 65 grade 2 IRRs were recorded in 45 (45%) patients. No grade 3-4 IRR was recorded. No local cutaneous reaction of grade 2 or more was recorded in patients in the SC rituximab group. In total, no difference was found between the IV group and the SC group in the rate of grade 2 IRRs (32% *vs*. 48%, $p = 0.25$). However, grade 2 IRRs were significantly more frequent in the SC rituximab group at the first IV rituximab infusion (32% *vs*. 11%, $p = 0.02$) and significantly less frequent in the SC rituximab group at the other seven rituximab administrations (4% *vs*. 43%, $p < 0.001$). The mean duration of the first IV rituximab infusion, which was common for both groups, was significantly higher in the SC rituximab group (6.1 ± 1.3 *vs*. 5.4 ± 2.1 hours, $p = 0.02$). The mean duration of subsequent infusion or injection was significantly lower in the SC rituximab group (1.5 ± 0.5 *vs*. 3.8 ± 0.5 hours, $p < 0.001$). The mean outpatient hospital length of stay for rituximab administration was significantly lower in the SC

rituximab group (16.4 ± 3.6 *vs*. 38.9 ± 5.9 hours, $p < 0.001$) even when excluding the first IV rituximab infusion (10.3 ± 3.2 *vs*. 33.5 ± 5.0 hours, $p < 0.001$).

Fifty non-IRR adverse events were collected for 45 (45%) patients, including 6 (6%) serious adverse events. The more frequent adverse event was reversible hematological grade 1 or 2 events in 35 (35%) patients. No grade 3 or 4 IRR was reported. Those hematological events led to chlorambucil dose reduction in 7 (7%) patients. Adverse events of infection were reported in 11 (11%) patients. Serious adverse events consisted of four serious adverse events of infection that required hospitalization with successful management without any sequelae, one patient was diagnosed with breast carcinoma and one patient had grade 3 neutropenia. There was no difference between the SC rituximab group and the IV rituximab group.

Discussion

Our study is the first to assess the effectiveness and safety of SC rituximab compared to IV rituximab in patients with GML. There was no significant difference between the formulations in terms of effectiveness and safety. The outpatient hospital length of stay and the IRR rate were significantly reduced in the SC rituximab group.

The efficacy of SC rituximab has been assessed in two large phase III studies and in one open-label cohort study in comparison with IV rituximab[9 24]. In those studies, the first cycle was administered intravenously to ensure the risk of IRR could be managed with infusion slowing down or interruption[12]. No difference was found between the two groups for complete, partial and overall response rates. In our study, we did not find any difference in overall response and complete remission rates between patients receiving IV formulations and those receiving SC formulations at weeks 6, 25 and 52 in an intent-to-treat manner.

Simplifying and shortening the preparation and administration of rituximab is highly beneficial to patients' burden and improves hospital resource utilization[12]. In our study, the mean outpatient hospital length of stay dramatically decreased in the SC rituximab group (16.7 ± 3.6 *vs*. 38.9 ± 5.9, $p < 0.001$) for the whole treatment and even more after excluding the first IV infusion, which was common to both groups (10.3 ± 3.3 *vs*. 33.4 ± 5.0, $p < 0.001$). As previously suggested, we strongly believe that extensive use of SC rituximab will contribute to better management of patients with GML[12].

IRRs are common in patients treated with rituximab [25]. The mechanisms involved in IRRs include cytokine release syndrome, tumor lysis syndrome and hypersensitivity reaction. IRRs are much more frequent during the first infusion and abruptly decrease with subsequent infusions. It is unclear whether patients with low grade or those with high-grade

lymphomas are at higher risk of IRR. In the SC rituximab development program, no difference was found in the safety profile of patients treated with SC or IV rituximab with the exception of an increased incidence of mild-to-moderate local cutaneous reactions. In our study, we reported a decrease in IRRs in patients treated with SC rituximab compared with those treated with IV rituximab when excluding the first IV infusion which was similar to both groups (4% *vs.* 43%, $p < 0.001$). No local cutaneous reaction of grade 2 or more was recorded in the SC rituximab group.

The retrospective nature of our study has inherent limitations. First, we did not assess grade 1 local cutaneous reactions on a prospective basis and we could not retrieve these data from case records. Second, we did not evaluate patient preference to ensure a decreased burden in patients treated with SC rituximab compared to IV rituximab. Last, we acknowledge a limited number of patients and potential selection bias common in tertiary care centers.

In conclusion, this retrospective study provides evidence of similar effectiveness and safety of the SC formulation of rituximab compared to the IV formulation in patients with GML. A cost-benefit analysis may be useful for a better understanding of the best choice of rituximab formulation in daily practice.

TABLES LEGENDS

Table 1: Baseline patient characteristics.

Table 2: Effectiveness results.

Table 3: Safety results.

References

1. Terada T. Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Ulcerative Colitis. *Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc*. 2014;20(5):319-322. doi:10.4103/1319-3767.141696

2. Thieblemont C. Clinical presentation and management of marginal zone lymphomas. *Hematol Am Soc Hematol Educ Program*. Published online 2005:307-313. doi:10.1182/asheducation-2005.1.307

3. Nakamura S, Sugiyama T, Matsumoto T, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. *Gut*. 2012;61(4):507-513. doi:10.1136/gutjnl-2011-300495

4. Zucca E, Copie-Bergman C, Ricardi U, et al. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol*. 2013;24 Suppl 6:vi144-148. doi:10.1093/annonc/mdt343

5. Zucca E, Conconi A, Martinelli G, et al. Final Results of the IELSG-19 Randomized Trial of Mucosa-Associated Lymphoid Tissue Lymphoma: Improved Event-Free and Progression-Free Survival With Rituximab Plus Chlorambucil Versus Either Chlorambucil or Rituximab Monotherapy. *J Clin Oncol*. 2017;35(17):1905-1912. doi:10.1200/JCO.2016.70.6994

6. Amiot A, Lévy M, Copie-Bergman C, et al. Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-

randomised observational study. *Aliment Pharmacol Ther*. 2014;39(6):619-628. doi:10.1111/apt.12635

7. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of H pylori in gastric MALT lymphoma. *Blood*. 2003;102(3):1012-1018. doi:10.1182/blood-2002-11-3502

8. Liu H, Ye H, Ruskone-Fourmestraux A, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. *Gastroenterology*. 2002;122(5):1286-1294. doi:10.1053/gast.2002.33047

9. Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017;4(6):e272-e282. doi:10.1016/S2352-3026(17)30078-9

10. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemi... - PubMed - NCBI. Accessed February 25, 2020. https://www.ncbi.nlm.nih.gov/pubmed/26947201

11. García-Muñoz R, Quero C, Pérez-Persona E, et al. Safety of switching from intravenous to subcutaneous rituximab during first-line treatment of patients with non-Hodgkin lymphoma: the Spanish population of the MabRella study. *Br J Haematol*. Published online October 1, 2019. doi:10.1111/bjh.16227

12. Davies A, Berge C, Boehnke A, et al. Subcutaneous Rituximab for the Treatment of B-Cell Hematologic Malignancies: A Review of the Scientific Rationale and Clinical Development. *Adv Ther*. 2017;34(10):2210-2231. doi:10.1007/s12325-017-0610-z

13. Stathis A, Gregorini A, Gressin R, et al. IELSG-38: A Phase II Study of Chlorambucil in Combination with Rituximab Followed By Maintenance Therapy with Subcutaneous Rituximab in Patients with Extranodal Marginal Zone B-Cell Lymphoma of Mucosa Associated Lymphoid Tissue (MALT). *Blood*. 2017;130(Supplement 1):1506-1506. doi:10.1182/blood.V130.Suppl_1.1506.1506

14. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition - WHO - OMS -. Accessed July 22, 2019. http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=70&codcch=4002

15. Musshoff K. [Clinical staging classification of non-Hodgkin's lymphomas (author's transl)]. *Strahlentherapie*. 1977;153(4):218-221.

16. Lévy M, Hammel P, Lamarque D, et al. Endoscopic ultrasonography for the initial staging and follow-up in patients with low-grade gastric lymphoma of mucosa-associated lymphoid tissue treated medically. *Gastrointest Endosc*. 1997;46(4):328-333.

17. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer*. 1983;52(8):1410-1416. doi:10.1002/1097-0142(19831015)52:8<1410::aid-cncr2820520813>3.0.co;2-3

18. Lévy M, Copie-Bergman C, Molinier-Frenkel V, et al. Treatment of t(11;18)-positive gastric mucosa-associated lymphoid tissue lymphoma with rituximab and chlorambucil: clinical, histological, and molecular follow-up. *Leuk Lymphoma*. 2010;51(2):284-290. doi:10.3109/10428190903431820

19. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood*. 2003;102(8):2741-2745. doi:10.1182/blood-2002-11-3496

20. Martinelli G, Laszlo D, Ferreri AJM, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2005;23(9):1979-1983. doi:10.1200/JCO.2005.08.128

21. Lévy M, Copie-Bergman C, Amiot A, et al. Rituximab and chlorambucil versus rituximab alone in gastric mucosa-associated lymphoid tissue lymphoma according to t(11;18) status: a monocentric non-randomized observational study. *Leuk Lymphoma*. 2013;54(5):940-944. doi:10.3109/10428194.2012.729832

22. Copie-Bergman C, Gaulard P, Lavergne-Slove A, et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. *Gut*. 2003;52(11):1656.

23. Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP. Accessed July 22, 2019. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

24. Lugtenburg P, Avivi I, Berenschot H, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. *Haematologica*. 2017;102(11):1913-1922. doi:10.3324/haematol.2017.173583

25. Paul F, Cartron G. Infusion-related reactions to rituximab: frequency, mechanisms and predictors. *Expert Rev Clin Immunol*. 2019;15(4):383-389. doi:10.1080/1744666X.2019.1562905

Table 1 : Baseline patient characteristics.

	Cases (n = 25)	Controls (n = 75)	Overall (n = 100)	*p*
Male, no. (%)	10 (40%)	27 (36%)	37 (37%)	0.81
Age, years	59.3 ± 15.1	59.2 ± 14.0	59.3 ± 14.5	0.92
BMI, kg/m²	25.7 ± 3.1	24.6 ± 4.2	25.1 ± 3.7	0.05
Hp positive, no (%)	8 (32%)	17 (23%)	25 (25%)	0.43
Translocation t(11;18), no (%)	9 (36%)	27 (36%)	36 (36%)	1.00
History of immunotherapy and/or chemotherapy, no. (%)	4 (16%)	12 (16%)	16 (16%)	1.00
Endoscopic appearance				
Pseudotumoral/ Large folds/Gastritis/Ulcer/pseudopolyp	12%/84%/0%/4%	13%/69%/9%/9%	13%/73%/7%/7%	0.34
Topography, no. (%)				
Antrum / Antrocorporeal junction / Corpus / Diffuse	8%/32%/60%	13%/40%/47%	12%/38%/50%	0.49
Extranodal involvement	2 (8%)	9 (12%)	11 (11%)	0.73
EUS, no. (%)				
gastric thickness > 5 mm	9/23 (39%)	29/74 (39%)	38 (39%)	1.00
gastric thickness > 10 mm	6/23 (26%)	14/74 (19%)	20 (21%)	0.56
Lymph nodes	11/23 (44%)	28/74 (37%)	39 (39%)	0.64
Disappearance of the layer structure	5 (22%)	11 (15%)	16 (17%)	0.52
Ann Arbor classification, no. (%)				
IE or IIE	21 (84%)	63 (84%)	84 (84%)	1.00
IIIE or IV	4 (16%)	12 (16%)	16 (16%)	1.00
Blood tests				
LDH, ULN	0.56 ± 0.15	0.67 ± 0.21	0.62 ± 0.19	<0.001
Hemoglobin, g/dl	13.3 ± 1.6	13.4 ± 1.1	13.3 ± 1.4	0.59
Beta2-microglobulin, ULN	1.0 ± 0.6	0.91 ± 0.28	0.94 ± 0.46	0.28
SUV max	4.5 ± 3.2	2.9 ± 1.0	3.7 ± 2.6	0.09
Type of treatment, no. (%)				
Rituximab alone	8 (32%)	24 (32%)	32 (32%)	1.00
Rituximab plus chlorambucil	17 (68%)	51 (68%)	68 (68%)	1.00

EUS, endoscopic ultrasonography ; LDH: lactate dehydrogenase ; SUV : maximum standardized uptake value on ^{18}F-fluorodeoxyglucose positron emission tomography; ULN: upper limit of normal.

Plus–minus values are means ± SD. P values for all categorical variables are based on a two-sided chi² test. P values for continuous variables are based on Mann-Whithney test.

Table 2: Effectiveness results.

	Cases (n = 25)	Controls (n = 75)	Overall (n = 100)	P
Complete remission				
At W6	8/18 (44%)	40/66 (61%)	48/84 (57%)	0.29
At W25	20/25 (80%)	51/75 (68%)	71/100 (71%)	0.32
At W52	18/23 (78%)	57/75 (76%)	75/98 (77%)	0.99
Overall response				
At W6	13/18 (72%)	55/66 (83%)	68/84 (81%)	0.32
At W25	24/25 (94%)	70/75 (93%)	94/100 (94%)	0.99
At W52	21/23 (91%)	67/75 (89%)	88/98 (90%)	0.99

W6: week 6; W25: week 25; W52: week 52. According to the GELA histological grading system, complete remission was defined as the combination of CR- and pMRD-scores and overall response as the combination of CR-, pMRD- and rRD scores. P values are based on a two-sided chi² test.

Table 3: Safety results.

	Control (n = 75)	Cases (n = 25)	Overall (n = 100)	P
Any adverse event, no (%)	59 (78.7%)	16 (64%)	75 (75%)	0.18
Serious adverse event, no (%)	3 (4%)	3 (12%)	6 (6%)	0.16
IRR adverse event				
Number of IRR, no	48	17	65	
-after the first infusion	8	8	16	
-after the remaining infusion/injection	40	9	49	
Patients with IRR, no (%)	36 (48%)	8 (32%)	44 (44.0%)	0.25
-after the first infusion	8 (11%)	8 (32%)	16 (16.0%)	0.02
-after the remaining infusion/injection	32 (43%)	1 (4%)	33 (33.0%)	<0.001
IRR serious adverse event	0	0	0	-
Outpatient hospital length-of-stay, mean ± SD (hours)	38.9 ± 5.9	16.4 ± 3.6	33.3 ± 11.1	< 0.001
Non-IRR adverse event				
Non-IRR adverse event, no (%)	35 (47%)	10 (40%)	45 (45%)	0.65
Non-IRR serious adverse event, no (%)	3 (4%)	3 (12%)	6 (6%)	0.16
Hematological, no (%)	30 (40%)	5 (20%)	35 (35%)	0.09
Dose reduction, no (%)	6 (8%)	1 (4%)	7 (7%)	0.68
Infectious complication, no (%)	7 (9.3%)	4 (16%)	11 (11%)	0.46

IRR: infusion/injection-related reaction; SD: standard deviation; P values are based on a two-sided chi^2 test.