Influence of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone on serologic parameters and clinical course in lymphoma patients with autoimmune diseases


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Background: As patients with B-cell lymphomas suffering from an underlying autoimmune condition undergoing therapy with the CD20 antibody rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) offer the unique possibility of monitoring effects of therapy on various rheumatologic parameters, we have evaluated serologic autoimmune markers and the clinical outcome of patients with autoimmune diseases (ADs) who received lymphoma treatment with R-CHOP during the course of their disease.

Patients and methods: We have retrospectively analysed 13 patients with non-Hodgkin’s lymphoma who concurrently suffered from ADs and were treated with the R-CHOP regimen. Subjective parameters along with rheumatoid factor (RF) and antinuclear antibodies (ANA) were serially measured.

Results: The median levels of RF were 901 IU/ml [inter-quartile-range (IQR) 189–2520] before and 75 IU/ml (IQR 45–644) after therapy (P = 0.028). The median levels of ANA were 800 (IQR 140–2560) before and 100 (40–1280) after therapy (P = 0.027). Ten (77%) patients showed clinical improvement of their autoimmune symptoms, two (15%) reported no difference and one (7%) patient with rheumatoid arthritis-related worsening symptoms during therapy with R-CHOP. The autoimmune-related symptoms recurred after a median time of 7 weeks (IQR 6–8) in seven patients. In terms of lymphoma response, 11 patients achieved a complete remission and two a partial remission.

Conclusions: This analysis indicates that R-CHOP given for lymphoma treatment is also effective for therapy of concurrent rheumatoid diseases. Both rheumatoid parameters as well as clinical symptoms showed a significant decrease during treatment with this immunotherapy. The effects on the rheumatic diseases, however, seem to be of limited duration.

Key words: autoimmune diseases, lymphoma, R-CHOP, rituximab

introduction

The development of a non-Hodgkin’s lymphoma (NHL) is one of the most serious complications in patients with autoimmune diseases (ADs) [1]. Most of these lymphomas originate from B cells with mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL) being the most common subtypes in these patients. At the moment, it is not known whether these lymphomas have a different clinical course or a different responsiveness to therapy compared with their counterparts in patients without AD. Chemotherapy, however, is the treatment of choice in this setting and the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was considered the standard of care in aggressive lymphomas until recently. The addition of rituximab (R), an anti-CD20 antibody, was recently shown to be capable of increasing the effectiveness of CHOP chemotherapy both in DLBCL [2] as well as in indolent lymphomas [3, 4]. CD20 is a surface antigen specific for B cells and is therefore a rational target for an antibody therapy with R.

On the other hand, B lymphocytes are not only the key target in NHL but also play an integral part in the pathogenesis of autoimmunity. It was indicated that targeting and blocking these cells may be beneficial in patients suffering from AD [5–7]. Furthermore, the beneficial effect of R in patients with active rheumatoid arthritis (RA) despite treatment with methotrexate (MTX) was clearly shown in a randomised, double-blind controlled trial [8].
In keeping with these findings, one might hypothesise that immunochemotherapy administered to treat lymphoma in patients with AD could potentially diminish (or even eradicate) autoreactive cell clones and might therefore improve the underlying autoimmune condition. As keystones of the R, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen, i.e. R, cyclophosphamide or prednisone, are currently used to treat autoimmune disorders, a beneficial effect of this regimen on the AD should be expected.

Due to the fact that patients with B-cell lymphomas suffering from an underlying autoimmune condition undergoing therapy with R-CHOP offer the unique possibility of monitoring effects of therapy on various rheumatologic parameters, we have retrospectively evaluated serologic autoimmune markers and the clinical outcome of patients with ADs who received lymphoma treatment with R-CHOP during the course of their disease.

patients and methods

We have retrospectively analysed 13 patients with NHL who concurrently suffered from ADs and were treated with the R-CHOP regimen (Table 1).

The various lymphoma subtypes were defined according to the criteria outlined in the recent World Health Organisation (WHO) classification [9]. Nine of our patients had MALT lymphoma, while four suffered from DLBCL. These nine patients with MALT lymphoma comprised 33% (i.e. nine out of 27) of patients given R-CHOP for relapse of their disease at our institution.

All patients were systematically asked for a previous diagnosis of AD or the presence and duration of symptoms indicative for an AD: (i) musculoskeletal complaints: arthralgia or arthritis and morning stiffness, myalgia and muscle weakness, and inflammatory back pain; (ii) dry eyes or dry mouth; (iii) UV sensitivity, skin rashes, purpura or skin thickening. When patients were previously diagnosed as having a rheumatic disease, a thorough review of their medical history was carried out including drug intake. At every visit, patients were asked for the presence of joint pain, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other ADs (Table 1).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex, age</th>
<th>Lymphoma</th>
<th>Rheumatic disease</th>
<th>RF</th>
<th>ANA</th>
<th>RD before NHL</th>
<th>RD duration before NHL</th>
<th>Immunomodulatory medication before lymphoma diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 89</td>
<td>MALT</td>
<td>RA</td>
<td>Neg</td>
<td>Pos</td>
<td>No</td>
<td>–</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F, 60</td>
<td>MALT</td>
<td>SS</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>5a</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>F, 54</td>
<td>MALT</td>
<td>DM</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>6a</td>
<td>CSA</td>
</tr>
<tr>
<td>4</td>
<td>M, 78</td>
<td>MALT</td>
<td>RA</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>13a</td>
<td>Gold, leflunomide</td>
</tr>
<tr>
<td>5</td>
<td>F, 84</td>
<td>MALT</td>
<td>RA</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>1a</td>
<td>Steroids</td>
</tr>
<tr>
<td>6</td>
<td>F, 73</td>
<td>MALT</td>
<td>RA</td>
<td>Pos</td>
<td>Neg</td>
<td>No</td>
<td>–</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>F, 87</td>
<td>MALT</td>
<td>Atopy</td>
<td>Neg</td>
<td>Pos</td>
<td>Yes</td>
<td>8a</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F, 71</td>
<td>DLBCL</td>
<td>RA</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>30a</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>F, 78</td>
<td>DLBCL</td>
<td>RA</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
<td>8a</td>
<td>MTX, steroids</td>
</tr>
<tr>
<td>10</td>
<td>F, 67</td>
<td>MALT</td>
<td>Sharp syndrome</td>
<td>ND</td>
<td>Pos</td>
<td>Yes</td>
<td>8a</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>11</td>
<td>M, 69</td>
<td>MALT</td>
<td>SS</td>
<td>Neg</td>
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<td>Yes</td>
<td>1a</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>F, 69</td>
<td>DLBCL</td>
<td>SLE</td>
<td>Neg</td>
<td>Pos</td>
<td>Yes</td>
<td>12a</td>
<td>Gold, chloroquine, steroids, CSA</td>
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<tr>
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<td>DLBCL</td>
<td>Vasculitis</td>
<td>Pos</td>
<td>Neg</td>
<td>Yes</td>
<td>14a</td>
<td>Steroids, MTX</td>
</tr>
</tbody>
</table>

RF, rheumatoid factor; ANA, antinuclear antibody; RD, rheumatic disease; NHL, non-Hodgkin’s lymphoma; M, male; MALT, mucosa-associated lymphoid tissue lymphoma; RA, rheumatoid arthritis; Neg, negative; Pos, positive; F, female; SS, Sjögren’s syndrome; DM, dermatomyositis; CSA, cyclosporine A; DLBCL, diffuse large B-cell lymphoma; MTX, methotrexate; ND, no data; SLE, systemic lupus erythematoses; –, not applicable.

Chemotherapy consisted of R given at the standard dose of 375 mg/m2 on day 1, while chemotherapy with the CHOP-regimen was given on day 2. According to our previous experience, chemotherapy was administered according to age in our patients. In patients younger than 75 years, standard CHOP consisting of cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2 and vincristine 1.4 mg/m2 (for a maximum single dose of 2 mg) was given intravenously (i.v.) on day 2 along with 100 mg oral prednisone on days 2–6 (CHOP). Patients older than 75 years received therapy at a reduced dose including cyclophosphamide 750 mg, doxorubicin 50 mg and vincristine 1 mg total dose i.v. on day 2 and prednisone 100 mg p.o. on days 2–6. Antiemetic prophylaxis with 5-HT3-receptor antagonists was administered on a routine basis. For initiation of chemotherapy, a left ventricular ejection fraction >50% as judged by echocardiography, a leucocyte count >3500/μl and a thrombocyte count >100 000/μl as well as normal liver and renal function parameters were required.

Cycles were repeated every 3 weeks with reevaluation of treatment response every three cycles. Response to treatment was classified according to the International Working Group recommendations [10]. In case of stable disease (i.e. less than 50% reduction and less than 50% increase in the sum of the products of the greatest diameters and no appearance of new lesions), partial regression or complete remission (CR) of the lymphoma upon reevaluation, treatment was continued for another three cycles up to a maximum of six cycles in the cohort of older patients, while younger patients received eight cycles.

The statistical analysis was done with the SPSS 12.0 program. Wilcoxon’s signed-rank test was used for comparison of pre- and posttreatment values. The manufacturer details for the drugs used for lymphoma treatment are: rituximab (Mabthera® from Roche), cyclophosphamide (Endoxan® from Baxter), vincristine (Oncovin® from Stada), doxorubicin (Doxorubicin® from Ebeewe) and prednisone (Aprednisol® from Merck).
results

A total of 13 patients were evaluated. Out of these 13 cases, nine patients were assessable before and after therapy, while two patients were lost to follow-up after completion of therapy and two patients died during the course of chemotherapy. All patients reported symptoms indicative of, or had a previous diagnosis of, an AD.

Six patients had RA, two Sjögren’s syndrome (SS), while one patient each suffered from vasculitis, dermatomyositis, Sharp syndrome, atopy and systemic lupus erythematosus. Eleven patients had AD before diagnosis of NHL while two patients presented with NHL and were found to have AD during the initial lymphoma staging. The median duration from initial diagnosis of an AD to lymphoma diagnosis was 8 years [inter-quartile-range (IQR) 5–13].

Eight out of 12 patients (66%) were RF positive and 11 out of 13 (84%) had elevated ANA at diagnosis of the lymphoma (Table 1).

Seven patients regularly received immunomodulatory drugs while two patients took drugs on demand (Table 1).

The median levels of RF were 901 IU/ml (IQR 189–2520) before and 75 IU/ml (IQR 45–644) after therapy ($P = 0.028$) (Figure 1). The median levels of ANA were 800 (IQR 140–2560) before and 100 (40–1280) after therapy ($P = 0.027$) (Figure 2). Figure 3 exemplifies a typical course of RF during treatment with MTX and R-CHOP.

Ten (77%) patients showed clinical improvement of their autoimmune symptoms during the course of R-CHOP treatment. Two (15%) patients reported no difference with regard to their AD and one (7%) patient who suffered from RA related a worsening of symptoms during R-CHOP. The autoimmune-related symptoms recurred after a median time of 7 weeks (IQR 6–8) in seven patients. One patient who previously suffered from vasculitis had a durable remission after completion of R-CHOP now ongoing for 20 months.

With regards to lymphoma response, 11 patients achieved a CR and two a partial remission (PR).

So far, one patient each achieving CR and PR, have relapsed from their lymphoma. These relapses were neither accompanied by an increase of autoimmune parameters nor a worsening of their rheumatoid symptoms.

As expected, side-effects of the R-CHOP regimen were moderate and mainly haematological. The predominant toxicity was leucocytopenia WHO grade 3 and 4 in seven and four patients, respectively.

Reactions to application of R were only mild with the standard premedication. The majority of patients experienced a transient fever and chills/rigors during the first R infusion which were managed by short discontinuation with consecutive slowing of the infusion rate. No recurrence of these symptoms was noted during the following infusions.

discussion

In accordance with previous studies about rheumatoid diseases and NHL, the large majority of our patients undergoing treatment with R-CHOP suffered from MALT lymphoma [1, 11]. Out of 27 consecutive patients given R-CHOP for relapsing MALT lymphoma, 33% (i.e. nine patients) had signs or a history of a rheumatoid disease. Four of these nine patients had a history of RA which is surprising because MALT lymphoma was hitherto reported to be associated with primary SS and Hashimoto thyroiditis but not with RA [1].

It has been a matter of debate whether the rheumatoid diseases constitute a paraneoplastic syndrome associated with the lymphoma [12] or if the lymphoma should be regarded as a long-term complication of the AD [1]. In our patient...
population, we noticed two groups which were clearly set apart from each other with regard to the duration of their ADs, >1 year versus >5 years. Therefore, it appears reasonable to indicate that autoimmune symptoms lasting <1 year before lymphoma diagnosis were triggered by the lymphoma rather than constituting a causative AD. In contrast to this are patients with a long history of AD (5–30 years) which may have triggered lymphoma development through chronic inflammation [13]. Interestingly, it was recently shown that the severity of the AD but not the previous medical treatment was associated with an increased risk for lymphoma development [1]. This finding is in agreement with the chronic inflammation theory for lymphoma development [13] and makes the assumption that lymphomas of patients with AD result mainly from long-term treatment with cytotoxic drugs, like MTX, relatively unlikely.

Our series also indicates that elevated autoimmune parameters in patients with MALT lymphoma are not merely a byproduct of the monoclonal B-cell proliferation without clinical relevance but that they are in fact associated with rheumatoid diseases in most cases. It would therefore be sensible to measure autoimmune parameters on a routine basis in patients with NHLs and in case of elevated values to search for underlying rheumatoid diseases. Appropriate therapy of the rheumatoid disease may slow down or even block the trigger (i.e. chronic inflammation) for lymphoma development.

Our results indicate that the R-CHOP therapy is not only effective for lymphoma treatment but also for the treatment of (underlying) rheumatoid diseases. Both autoimmune parameters and clinical symptoms were significantly improved by R-CHOP. This result is in accordance with a recent study which also indicated a beneficial effect of R-CHOP on both the lymphoma and the underlying AD [14]. In fact, important compounds of the regimen, such as cyclophosphamide and prednisone, are already widely used as single agents in the treatment of rheumatoid diseases. An entirely new approach to patients with ADs, however, is the use of the monoclonal anti-CD20 antibody R. As B cells have been recently demonstrated to play an important role in the pathogenetic pathways of rheumatoid diseases [15–17], their suppression or even eradication appears to be a reasonable therapeutic approach [18]. Since B cells play an important role in both, ADs and lymphoproliferative disorders, R appears to be an attractive therapeutic approach in lymphoma patients with concurrent ADs [19]. A recently published study showed that R is effective in the treatment of primary SS and MALT lymphoma associated with primary SS [20]. In contrast to data obtained in treating lymphomas with R, the authors found an unexplainably high incidence of human antichimeric antibodies [20]—a phenomenon which requires further investigations. Though we can assume most safety data from the long-term experience in the treatment of NHL, we do not know the most effective treatment schedule of R. At the moment, there is an ongoing debate about the best treatment schedule of R in the maintenance therapy of NHL. Pharmacokinetic studies, however, showed that considerable serum antibody levels are measurable for about 2–3 months and decline thereafter rapidly [21, 22]. In our series, this is within the median recurrence time of rheumatoid symptoms (7 weeks) which would indicate that R infusions should be repeated within a timeframe not longer than 2 months, at least in patients with AD.

While our series shows R-CHOP as effective treatment of AD, the nature of our retrospective series does not allow for extrapolation of a beneficial role of CHOP in addition to already demonstrated activity of R. Judging from the literature,
however, the time to symptom recurrence in our series seems to be equal or even shorter when compared with studies administering R alone [23]. Seven out of eight patients who showed an initial improvement complained about recurring rheumatic symptoms 6–8 weeks after finishing R-CHOP treatment. Repeated measurements of RF in one patient with RA showed a time–concentration pattern of RF, without lymphoma relapse, comparable with the administration of MTX (Figure 3). This temporary benefit is in keeping with the notion that application of R-CHOP does not result in permanent eradication of autoreactive cells. Therefore, autologous stem-cell transplantation after high-dose chemotherapy is currently investigated to eradicate autoreactive cells and early results seem to be promising [24, 25].

In conclusion, our study indicates that R-CHOP given for lymphoma treatment is also effective in the treatment of concurrent AD. Both rheumatoid parameters as well as clinical symptoms are decreasing during treatment with this immunomodulatory therapy. These effects, however, appear to be of short duration and warrant further investigation to optimise treatment approaches.

references