High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication

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Background: Rituximab is associated with low incidence of hypogammaglobulinemia and little morbidity. Our experience with the combination of rituximab + chemotherapy suggested the opposite.

Patients and methods: We analyzed our experience with rituximab plus chemotherapy in 97 patients to determine: frequency and type of non-neutropenic infection (NNI); frequency and type of hypogammaglobulinemia; response to gammaglobulin therapy; and factors associated with NNI.

Results: We observed 40 episodes of NNI in 19 of 97 (20%) patients. By 3 years, 43% of patients treated with rituximab + chemotherapy were projected to have developed at least one NNI. Of 19 with NNI, 15 had Ig levels studied and all 15 had hypogammaglobulinemia. Most frequently affected Ig were IgG (14 of 15) and IgM (13 of 14). IgA was usually spared (six of 14 cases affected). NNIs observed were 18 bronchitis, 16 sinusitis, four pneumonias, three otitis media, two fevers of unknown origin (FUOs) and three herpes zoster. Hospitalization was required in seven of 19. Ten received gammaglobulin infusions and all responded promptly. Gammaglobulin was given only when NNIs recurred. We examined sex, age, histology, type of rituximab–chemotherapy (fludarabine + rituximab versus other chemotherapy + rituximab) for correlation with NNI.

Conclusions: Indolent histology, female sex and fludarabine + rituximab significantly correlated with frequency of NNI but multivariate analysis picked fludarabine + rituximab followed by female gender as the only two independent variables predictive of NNI.

Key words: rituximab, non-Hodgkin’s lymphoma, hypogammaglobulinemia, fludarabine

introduction

As a therapeutic monoclonal antibody devised to eradicate CD20+ B lymphocytes, rituximab would be expected to induce hypogammaglobulinemia as a common side-effect. Yet in the pivotal single agent rituximab trial, hypogammaglobulinemia occurred in only 14% of cases and was not considered to be associated with any clinical morbidity [1]. However, our impression with the use of the combination of rituximab + cytotoxic chemotherapy was that non-neutropenic infections (NNI) associated with hypogammaglobulinemia occurred more commonly than with single agent rituximab. Furthermore, it is our impression that this side-effect frequently goes unrecognized by clinicians.

In order to determine objectively the frequency of NNIs, we analyzed our experience with the use rituximab plus chemotherapy to determine: frequency and type of non-neutropenic infections; frequency, severity and type of hypogammaglobulinemia; response to gammaglobulin infusion therapy; and factors associated with development of NNI.

patients and methods

We identified from our database, a total of 97 patients treated with rituximab in combination with cytotoxic chemotherapy at the Auxilio Mutuo Cancer Center in San Juan, Puerto Rico from 1 September 2002 to 30 June 2005. Nineteen patients had been treated elsewhere before referral to our center and 14 of these were in their first remission at the time of referral. Of those 97 patients, 77 were previously untreated and 20 previously treated. Of those previously treated, 13 had received CHOP (chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone) in the past, two had received fludarabine only, one had received CHOP and fludarabine and one MINE (mitoguazone, ifosfamide, vinorelbine and etoposide) plus fludarabine. We reviewed their medical records retrospectively to determine how many developed NNI. In addition, we recorded their pretreatment factors such as histology, age, gender, type of chemotherapy used and incidence, as well as type of infections.

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We also examined the frequency, type and severity of hypogammaglobulinemia as well as the response to intravenous gammaglobulin therapy.

Cases of bronchitis, sinusitis or pneumonia of acute onset and lasting over 2 weeks in spite of antibiotics or relapsing immediately after discontinuation of antibiotics and not associated with an absolute neutrophil count <1000, were considered as NNI. Others counted as NNI were any infections requiring hospitalization in spite of neutrophils >1000 and herpes zoster.

results

Of the 97 patients studied, 40 had an indolent histology (22 follicular grade 1–2, 12 small lymphocytic, three MALT, two splenic marginal zone lymphoma and one lymphoplasmaacytic) while 57 had an aggressive cell type (43 diffuse large cell, six follicular large, four mantle, three Burkitt, one unspecified).

Nineteen patients out of 97 (20%) with a median age of 58, developed a total of 40 episodes of NNI. A Kaplan–Meier cumulative estimate revealed that by 3 years, 43% of patients treated with rituximab + chemotherapy were projected to have developed at least one NNI (Figure 1).

In order to explore the correlation between several pretreatment factors and the development of NNI, we examined sex, age (<60 versus ≥60), histology (indolent versus aggressive), type of rituximab–chemotherapy (fludarabine + rituximab versus other chemotherapy + rituximab) and prior therapy (yes/no) as prognostic features. We identified indolent histology, female sex and fludarabine + rituximab as significant factors that correlated with the development of NNI at P < 0.05 (see Table 1). However, multivariate analysis[2] picked fludarabine + rituximab (P = 0.0007) followed by female gender (P = 0.026) as the only two independent variables predictive of NNI. Indolent histology, although significant in the univariate analysis, was excluded by multivariate analysis because of its strong correlation with the use of fludarabine + rituximab.

Females who received fludarabine + rituximab had a 63% (10 of 16) frequency of NNI versus only 10% (1 of 10) in males (P = 0.01).

Figure 2 illustrates the cumulative incidence of NNI according to type of rituximab + chemotherapy regimen utilized. Patients who received a fludarabine–rituximab combination had a much higher cumulative incidence of NNI than those treated with non-fludarabine–rituximab regimens. The most commonly used non-fludarabine–rituximab regimen was rituximab–CHOP, which was used in 77% of those cases, while the most common fludarabine–rituximab combination was fludarabine, mitoxantrone and dexamethasone (FND) [3], which was utilized in 85% of such patients. Of the 19 patients with NNI, serum quantitative immunoglobulin levels were determined in 15. All 15 subjects studied had hypogammaglobulinemia of at least one of the three gammaglobulin components studied (IgG, IgA, IgM). The most frequently affected immunoglobulins were IgM (13 of 14 = 93.3%) and IgG (14 of 15 = 92.8%). IgA was low in only six of 14 cases (42.8%).

In the cases that had hypogammaglobulinemia, the most profoundly affected immunoglobulin was IgM whose median level was 43% below the lower limit of normal. The second most profoundly affected was IgG with a median of 78% below the
intravenous immunoglobulin was usually very effective. As long as 6–12 months after administration. Retreatment with gammaglobulin infusions were repeated only when NNIs of the 12 treated with intravenous gammaglobulin, five 12 responded with complete resolution of their NNI. However, gammaglobulin as therapy for their first episode of NNI. All hospitalization. Twelve patients received 30 g intravenous Some patients had combined episodes of different types of two fevers of unknown origin (FUOs) and three herpes zoster. The changes in circulating B cells were studied over time in Czuczman et al. [7] observed depletion of B lymphocytes when treatment and none of the 34 patients developed serum immunoglobulins were monitored during and after treatment and none of the 34 patients developed hypogammaglobulinemia. Since we did not obtain quantitative immunoglobulin levels uniformly on all patients, it is impossible to tell how frequently this complication occurred, but it is very likely that this is a common complication hypogammaglobulinemia occurred more commonly in females remains unanswered. Similarly, why treatment with fludarabine and rituximab secondary to fludarabine–rituximab commonly affects the levels of IgG and IgM but usually spares IgA cannot be explained.

Other investigators [7–9] have also explored the combination of fludarabine–rituximab in lymphoma but have not described a high incidence of either NNI or hypogammaglobulinemia. Czuczman et al. [7] observed depletion of B lymphocytes when the changes in circulating B cells were studied over time in patients receiving this combination. Median B-cell levels reached low–normal range (10th percentile) at approximately 12–18 months post-therapy but some remained below the 10th percentile for a longer time. Interestingly, the quantitative serum immunoglobulins were monitored during and after treatment and none of the 34 patients developed hypogammaglobulinemia. It is not clear for how long the quantitative serum immunoglobulin levels were followed and perhaps if the follow-up was not long enough, some cases of hypogammaglobulinemia could have escaped detection since in many instances in our study this happened more than 1 year after treatment started. The NNIs observed in our study were not only of late onset but in addition, some were subtle in nature, consisting mostly of protracted upper respiratory infections. If the clinicians had not been aware of this, many of these NNIs might not have been identified as secondary to therapy. Another possible explanation for the frequent NNIs in our patients is that steroids were given to all but one of our observation is that in the ‘other chemotherapy’ group, there were very few events after 6 months (Figure 2), while in the fludarabine-treated group, most of the events occurred later on suggesting that the effect of fludarabine–rituximab is cumulative in nature. When an NNI occurs, it appears to be uniformly associated with hypogammaglobulinemia. It is not possible to determine if any of the 20 previously treated patients might have had hypogammaglobulinemia before receiving rituximab. However, the fact that they had not developed NNIs prior to receiving rituximab suggests, but does not prove, that this is not the case. Fludarabine was initially thought to be mostly associated with depletion of normal T lymphocytes [5]. However, recent studies in patients with psoriatic arthritis have shown that it is also associated with prominent depletion of normal B cells [6], which perhaps should have been anticipated in view of its known antitumor activity against B cell lymphoproliferative disorders such as chronic lymphocytic leukemia and low grade non-Hodgkin’s lymphoma. In addition, T cell depletion can result in decreased helper T cells, which are necessary for B cell maturation. Thus, profound T cell depletion induced by fludarabine, and combined with B cell depletion secondary to fludarabine and rituximab, can lead to severe hypogammaglobulinemia. In this sense, it should not be surprising that the combination of rituximab and fludarabine results in a high incidence of NNI associated with hypogammaglobulinemia. Since we did not obtain quantitative immunoglobulin levels uniformly on all patients, it is impossible to tell how frequently this complication occurred, but it is very likely that this is a common complication since some patients that develop hypogammaglobulinemia might not necessarily develop infections. Exactly why hypogammaglobulinemia occurred more commonly in females remains unanswered. Similarly, why treatment with fludarabine–rituximab commonly affects the levels of IgG and IgM but usually spares IgA cannot be explained.

discussion
Neither the single-agent pivotal trial of salvage rituximab for indolent NHL [1] nor the front-line trial of the CHOP–rituximab combination [4] identified non-neutropenic infections as a major problem. Hypogammaglobulinemia, as a consequence of rituximab therapy, was seen in only 15% of cases in the pivotal trial and there were no significant clinical sequelae even when this was observed.

This report summarizes our experience with the use of rituximab in combination with either fludarabine or non-fludarabine based regimens. Our experience strongly suggests that when rituximab is combined with fludarabine, the incidence of NNI is very high as compared with non-fludarabine-based rituximab combinations. An interesting
patients who received fludarabine–rituximab while none of the patients in the other fludarabine containing studies received steroids. Finally, we cannot rule out an ethnic predisposition to the development of hypogammaglobulinemia since essentially all of our patients were from Puerto Rico.

Prolonged exposure to single agent rituximab would also be expected to produce B cell depletion of long duration. We would expect that maintenance therapy with rituximab would be associated with hypogammaglobulinemia. In order to find data on this subject, we conducted a literature search on maintenance rituximab and found five articles [10–14]. All of these studies used maintenance rituximab strategies and all were carried out using single-agent rituximab. However, the only manuscript that addressed the issue of hypogammaglobulinemia was the study by Ghielmini et al. [15] in which they examined the B lymphocyte count and analyzed the IgM level after single-agent induction therapy with 4 weekly rituximab doses versus the same induction followed by maintenance every 2–4 months. They found that B-cell levels decreased during the induction phase and remained low in the maintenance arm. This was accompanied by a reduction of the IgM levels at 86% and 72% of baseline. However, they did not provide data on the percentage of patients who actually developed hypogammaglobulinemia. They do state that the incidence of adverse events was not increased with their maintenance single-agent strategy, thus suggesting that perhaps the combination of fludarabine and rituximab is more prone to result in severe hypogammaglobulinemia and NNI than the prolonged use of rituximab as a single agent.

The infections observed in this study were consistent with those seen in cases of congenital or acquired hypogammaglobulinemia and ranged from mild but protracted cases of sinusitis, bronchitis and otitis media to more serious problems requiring hospitalization such as pneumonia and fever of unknown origin. In order to avoid the common confounding effect of neutropenia induced by chemotherapy, we only included non-neutropenic infections in this study. However, it is very likely that some neutropenic infections that occur with the fludarabine–rituximab combination might be aggravated by the additional morbidity caused by hypogammaglobulinemia.

In summary, we observed an exceedingly high incidence of NNI associated with hypogammaglobulinemia in patients treated with rituximab plus chemotherapy, and particularly with the fludarabine–rituximab combination. This can lead to significant morbidity including hospitalizations and is usually manifested as either bronchitis, sinusitis, pneumonia, otitis media, herpes zoster and non-neutropenic FUO, frequently of delayed onset. For reasons that remain unclear, females who receive fludarabine–rituximab are more prone than males to develop this complication (incidence is 63% in females versus 10% in males, \( P = 0.01 \)). A prospective study would be desirable in order to confirm and extend these findings. Finally, it is important that clinicians recognize this complication because it can be treated effectively with intravenous immunoglobulins.

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references