Abstract

Purpose: T cells influence outcome in follicular lymphoma, but their contributions seem to be modified by therapy. Their impact in patients receiving rituximab without chemotherapy is unknown.

Experimental Design: Using flow cytometry, we evaluated the T cells in tumors and/or blood in a total of 250 follicular lymphoma patients included in two Nordic Lymphoma Group randomized trials that compared single rituximab with IFN-α2a–rituximab combinations.

Results: In univariate analysis, higher levels of CD3⁺, CD4⁺, and CD8⁺ T cells in both tumors and blood correlated with superior treatment responses, and in multivariate analysis, tumor-CD3⁺ (P = 0.011) and blood-CD4⁺ (P = 0.029) cells were independent. CD4⁺ cells were favorable regardless of treatment arm, but CD8⁺ cells were favorable only in patients treated with single rituximab, because IFN-α2a improved responses especially in patients with low CD8⁺ cell levels. Higher levels of blood-CD3⁺ (P = 0.003) and blood-CD4⁺ (P = 0.046) cells predicted longer overall survival, and higher levels of blood-CD8⁺ cells longer times to next treatment (P = 0.046).

Conclusions: We conclude that therapeutic effects of rituximab are augmented by tumor-associated T cells for rapid responses and by systemic T cells for sustained responses. CD4⁺ and CD8⁺ cells are both favorable in patients treated with rituximab. IFN-α2a abrogates the negative impact of few CD8⁺ cells. Clin Cancer Res; 17(12); 4136–44. ©2011 AACR.

Introduction

Immune cells in the tumor microenvironment influence outcome in follicular lymphoma (1–15). High levels of CD8⁺ T cells have been associated with good prognosis (5–7) and high levels of CD4⁺ T cells mostly with poor prognosis (4, 7–9). However, the prognostic importance of the immune microenvironment seems to be modified by therapy (15). Addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy has been shown to cancel the hitherto negative impact of macrophages (13, 14). In patients receiving rituximab without chemotherapy, the contribution of the microenvironment is unknown. Likewise, blood lymphocyte subsets have been little studied in follicular lymphoma.

Rituximab is nowadays included in all standard, first-line regimens against follicular lymphoma, with or without concomitant chemotherapy (16, 17). Many of the clinico-biological effects of rituximab are probably dependent on T cells of both the CD4 and the CD8 lineage (18). We therefore hypothesized that high pretreatment levels of both CD4⁺ and CD8⁺ cells in the tumor microenvironment as well as in the blood are advantageous for the response to rituximab. IFN-α2a (here onward used as IFN-α), another drug used in follicular lymphoma, alters and potentiates immune cells of importance for antibody-dependent cellular cytotoxicity (ADCC) against the rituximab-binding lymphoma.

To test the CD4 and CD8 hypothesis and to find rituximab-specific biological predictors for response, we investigated the lymphocyte populations in tumors and blood.
from follicular lymphoma patients participating in 2 Nordic Lymphoma Group (NLG) randomized trials evaluating rituximab with or without the addition of IFN-α.

Materials and Methods

Patients and treatment

We studied patients participating in 2 clinical NLG trials M39035 (ref. 19; phase II, accrual 1998–1999) and ML16865 (phase III, accrual 2002–2008). All patients received rituximab and were 1:1 randomized to the addition of IFN-α. Inclusion criteria were symptomatic, advanced, indolent CD20+ lymphoma, previously untreated or in first relapse after a previous response to only oral alkylators or local radiation. The previous treatment was completed at least 6 months before inclusion and it had low potential to affect immune cells in this report because it had mostly been given a long time before trial inclusion: 33 of 57 previously treated patients in this report had finished treatment at least a year (and up to 17 years) before trial inclusion. The 2 trials had similar outlines (Fig. 1). Response was evaluated after the first and the second cycle, each consisting of 4 doses of rituximab (375 mg/m²) with or without IFN-α. In M39035, patients with partial or minor response at first response evaluation (EV-1) were randomized to receive the second cycle with or without IFN-α. In ML16865, IFN-α was randomized upfront. In both studies, patients with stable or progressive disease at EV-1 were not eligible for the second cycle. In M39035, 126 (92 follicular lymphoma) patients and in ML16865, 313 (259 follicular lymphoma) patients were included, making a total of 439 (351 follicular lymphoma) patients. All diagnostic specimens were reviewed by C.S. The patients were studied according to trial protocols approved by the ethics committee at each participating center, and patients provided written informed consent. Flow cytometric analyses of prestudy treatment samples of blood and tumors were recommended in the trial protocols, but not obligatory, and conducted in 250 of 351 follicular lymphoma patients at inclusion. There was no selection of patients for flow cytometry. No differences in the Follicular Lymphoma International Prognostic Index (FLIPI; ref. 20), treatment responses, or survival times were found between the 250 patients analyzed and the 101 not analyzed with flow cytometry.

Figure 1. Trial schemata of M39035 and ML16865. Week 10 for EV-1 and week 16 for EV-2 were counted from the patient’s first dose of rituximab in the respective cycle. Each gray rectangle symbolizes a weekly dose of 375 mg/m² rituximab and each black zigzagged line represents IFN-α at 3 MIU/d during week 1 and 4.5 MIU/d (except rituximab days) during weeks 2 through 5. EV-1 and EV-2, first and second treatment response evaluation.

Translational Relevance

Previous studies of the microenvironment in follicular lymphoma have correlated CD8+ T cells with good prognosis and CD4+ T cells with poor. Most patients in those studies were treated before the introduction of rituximab, which is nowadays part of standard treatment. Because some of the antilymphoma activities of rituximab may be dependent on CD4+ and CD8+ cells, both subsets could be favorable in the rituximab setting. We used prospectively recorded flow cytometric analyses from 2 randomized trials where all patients received single rituximab or IFN-α–rituximab combinations. T cells (both CD4+ and CD8+) in tumors were associated with quick and good rituximab responses, whereas T cells in blood correlated with slower but good and sustained rituximab responses and were more important for survival. IFN-α abrogated the dependence on high CD8+ numbers (in both blood and tumors) for a good rituximab response. We believe our findings suggest a future of personalized therapy based on biological characteristics of the patients.
Flow cytometric method

The participating flow cytometric laboratories used standardized protocols for analysis of the samples in the trials. Lymphocyte subset levels were reported as percentages of the population within the mononuclear gate. Analyzed lymphocyte subsets in the present article were T (CD3+, CD4+, and CD8+), natural killer (CD56+ (in blood only)), and B cells (CD19+). A full description of the flow cytometric method is given in Supplementary Data. The subset numbers were prospectively recorded in the case report forms of the 2 trials. Tumor specimens were obtained in 187 of 250 patients, blood specimens in 184 of 250 patients, and both types of specimen in 121 of 250 patients. For this study, the data from case report forms were validated by B.E.W., using the original flow cytometric reports. There was almost total agreement between case report forms and source data (data not shown).

Treatment response

Responses in both trials were categorized according to the 1999 Cheson criteria (21): complete (CR), complete/unconfirmed (CRu) and partial (PR) response, and stable (SD) and progressive disease (PD). An additional subcategory of SD, minor response (MR), was used at EV-1 only to allow patients to enter cycle 2. MR was defined as a decrease in the sum of the products of the greatest diameters in all measurable lesions of at least 25% but less than 50% from baseline and/or improvement of disease symptoms. Response data were available in 248 of 250 patients at EV-1 and at the second response evaluation (EV-2), in 177 of 180 patients allocated to the second cycle.

Statistical methods

Treatment response was used as the main endpoint, but the long follow-up times also allowed for survival analysis. The poor response category was defined as MR, SD, or PD, the middle response category as PR, and the good response category as CR or CRu. To avoid bias from supervised cutoff point determination, immune cell levels were tested as continuous variables, except in survival analysis, where they were grouped by the 25th, 50th, and 75th percentiles. Associations with response were estimated with Wilcoxon/Kruskal–Wallis and Spearman tests, depending on the nature of the variables. Significant factors competed in multivariate, forward, stepwise, ordered logistic regression. The lymphocyte subsets were also estimated for collinearity and for associations with the FLIPI. Time to next treatment and overall survival were calculated from the date of trial inclusion to the date of off-study antilymphoma treatment (time to next treatment) or death (overall survival). Patients were censored at last follow-up (September 2009). Associations with time to next treatment and overall survival were evaluated using Kaplan–Meier curves and the log-rank test. Multivariate analysis was conducted with forward stepwise Cox regression. All \( P \) values are 2-tailed and

### Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic category</th>
<th>( N (%) )</th>
<th>Association with response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EV-1</td>
<td>EV-2</td>
</tr>
<tr>
<td></td>
<td>OR ( P )</td>
<td>OR ( P )</td>
</tr>
<tr>
<td>Male sex</td>
<td>129 (52)</td>
<td>1.8 0.019</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>84 (34)</td>
<td>1.4 0.24</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28 (11)</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>79 (32)</td>
<td>0.4 0.7</td>
</tr>
<tr>
<td>IV</td>
<td>141 (57)</td>
<td>0.5 0.62</td>
</tr>
<tr>
<td>Involved nodal areas &gt; 4</td>
<td>125 (50)</td>
<td>0.8 0.46</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/dL</td>
<td>53 (21)</td>
<td>1.5 0.19</td>
</tr>
<tr>
<td>LDH elevated</td>
<td>62 (25)</td>
<td>1.5 0.17</td>
</tr>
<tr>
<td>FLIPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 (low risk)</td>
<td>72 (29)</td>
<td>1</td>
</tr>
<tr>
<td>2 (intermediate risk)</td>
<td>83 (33)</td>
<td>0.7 1.0</td>
</tr>
<tr>
<td>3–5 (high risk)</td>
<td>94 (38)</td>
<td>1.2 0.48</td>
</tr>
<tr>
<td>Lymphoma in bone marrow</td>
<td>115 (50)</td>
<td>1.2 0.41</td>
</tr>
<tr>
<td>Bulk &gt; 10 cm</td>
<td>40 (16)</td>
<td>1.4 0.34</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>193 (77)</td>
<td>1</td>
</tr>
<tr>
<td>Local radiation</td>
<td>18 (7)</td>
<td>2.0 0.7</td>
</tr>
<tr>
<td>Alkylators</td>
<td>30 (12)</td>
<td>1.8 1.8</td>
</tr>
<tr>
<td>Both</td>
<td>9 (4)</td>
<td>0.7 0.15</td>
</tr>
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</table>

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of the FLIPI-constituting factors, most correlations were weakly (median of 55.7% (Table 2). The t-CD3 and b-CD3 correlated with better treatment responses at EV-1 and EV-2 but t-CD4 only at EV-1 (Table 2). Higher t-CD19 levels were associated with inferior responses only at EV-1. Blood subsets did not affect responses at EV-1, but at EV-2 both b-CD3 and b-CD4 were positively associated with superior responses. The b-CD19 [median: 7.0% (p25, 3.0%; p75, 19.1%); n = 172] and b-CD56 [median: 17.4% (p25, 9.1%; p75, 25.7%); n = 137] had no bearing on responses at EV-1 nor at EV-2. Neither did the t-CD4/CD8 [median: 3.6 (p25, 2.6; p75, 5.1)] nor b-CD4/CD8 [median: 1.3 (p25, 0.9; p75, 1.8)]. These analyses were repeated, stratified by previous treatment, showing similar trends as above, although fewer observations reduced significance (data not shown). Absolute lymphocyte blood counts did not predict treatment response, neither did absolute T-cell blood counts, similar to a previous study (22).

Multivariate analysis of treatment response

Factors significant in univariate analysis, plus the FLIPI and previous therapy, competed in multivariate analysis with respect to response. At EV-1, the only independent factor was t-CD3 (P = 0.003). At EV-2, t-CD3 (P = 0.011), b-CD4 (P = 0.029), and age more than 60 years (P = 0.001) were independent (Table 3).

Analysis of best response

As shown in Figure 1, patients in M39035 with CR at EV-1 did not continue to cycle 2, which could have affected the EV-2 analysis. Therefore, a best response analysis was conducted with respect to achieving CR/CRu at either EV-1 or EV-2. Predictive factors for best response were similar to those at EV-2 in univariate analysis (data not shown) and in multivariate analysis, the same predictors as at EV-2 were independent: t-CD3 (P = 0.036), b-CD4 (P = 0.009), and age more than 60 years (P = 0.015).

T cells and randomization to IFN-α

Patients treated with combinations of rituximab and IFN-α showed better responses at EV-2 than patients given single rituximab (Fig. 2). High pretreatment levels of t-CD8 (EV-1, P = 0.009; EV-2, P = 0.031) and b-CD8...
(EV-2, \( P = 0.016 \)) correlated with better responses in patients treated with single rituximab. The t-CD8 and b-CD8 had no effect in those treated with IFN-\( \alpha \)-rituximab. The effects of CD4\(^{+} \) cells seemed more evenly distributed in both strata of randomization. The t-CD4 were significant in patients treated with single rituximab (EV-1, \( P = 0.022 \)). The b-CD4 were significant in IFN-\( \alpha \)-rituximab-treated patients (EV-2, \( P = 0.017 \)) and showed a trend in single rituximab-treated patients (EV-2, \( P = 0.051 \)). In patients given IFN-\( \alpha \)-rituximab, higher t-CD4/CD8 (EV-1, \( P = 0.019 \)) and b-CD4/CD8 (EV-2, \( P = 0.031 \)) correlated with better responses. In multivariate analysis of the subset of patients given single rituximab, t-CD8 were independent at EV-1 (\( P = 0.004 \)) and b-CD8 at EV-2 (\( P = 0.027 \)). In patients treated with IFN-\( \alpha \)-rituximab, only t-CD4/CD8 were significant at EV-1 and b-CD4 were independent at EV-2 (\( P = 0.032 \)). Moreover, in patients with high (\( \geq 1.3 \)) b-CD4/CD8, IFN-\( \alpha \) had a significant effect (EV-2, \( P = 0.006 \)) but not in patients with low (<1.3) b-CD4/CD8 (EV-2, \( P = 0.9 \)). Similarly, the effect of IFN-\( \alpha \) was significant (EV-2, \( P = 0.013 \)) in patients with low (<23.2% median) b-CD8 but not in those with high (\( \geq 23.2 \)) b-CD8 (EV-2, \( P = 0.9 \)).

**Survival analysis**

Of the 250 patients, 152 had received off-study treatment and 40 had died at the time of this analysis. The median follow-up time was 3.3 years, and the median overall survival time was not reached. The overall survival rate at 5 years was 82%. The median time to next treatment was estimated to be 2.2 years. The failure-free rate with respect to time to next treatment at 5 years was 29%. The FLIPI was predictive for overall survival (\( P = 0.0002 \)) and time to next treatment (\( P = 0.002 \)). The quality of the treatment response at EV-1 showed a strong association with overall survival (\( P = 0.006 \)). Higher b-CD3 correlated with longer overall survival (\( P = 0.003 \)). Median overall survival was 7.9 years in patients with less than 55.7% of b-CD3 and not reached in patients with 55.7% or more of b-CD3 (Fig. 3A). Also higher b-CD4 had a significant association with overall survival (\( P = 0.046 \)), whereas higher b-CD8 correlated with longer time to next treatment (\( P = 0.046 \)). Median time to next treatment in patients with less than 23.2% of b-CD8 was 1.8 years and 2.7 years in patients with 23.2% or more of b-CD8 (Fig. 3B). With respect to time to next treatment, b-CD3 and b-CD4 had borderline associations (\( P = 0.059; P = 0.066 \)). No tumoral lymphocyte subsets or ratios were associated with time to next treatment or overall survival. In multivariate overall survival analysis, b-CD3 (\( P = 0.008 \)) and quality of response at EV-1 (\( P = 0.0002 \)) remained independent (\( n = 152 \)).

**Discussion**

Several immune cell subsets in the follicular lymphoma microenvironment have been associated with outcome (1–15). However, many types of therapy have been used in these various cohorts of follicular lymphoma patients, with different effects on tumor cells and possibly also on non-malignant cells within the tumor microenvironment (15). The addition of rituximab to chemotherapy has been shown to alter the impact of macrophages (13, 14). We now show that the composition of the systemic as well as the local immune system may influence outcome in follicular lymphoma patients given rituximab without chemotherapy. In the present study, prospective flow cytometric analyses were conducted in 250 follicular lymphoma patients entering 2 clinical trials consisting of 2 cycles (in total, 8 doses) of rituximab with a randomization to additional IFN-\( \alpha \). Our results, showing prediction from pretreatment levels of immune cells in the tumor microenvironment and in the blood, are the first from a large cohort treated with biological agents only.

In the tumor microenvironment, t-CD3, t-CD4, and t-CD8 correlated with better responses already at EV-1, after 4 doses of rituximab. The total number of tumor T cells (t-CD3) was independent in multivariate analysis both at EV-1 and at EV-2. Together with the univariate analyses, this suggests that both t-CD4 and t-CD8 have a favorable effect. Tumor-associated CD4\(^{+} \) T cells have been associated with poor prognosis in follicular lymphomas from the pre–rituximab era (7–9). The present study suggests that the unfavorable impact from high t-CD4 is reversed by rituximab, similar to what has been shown for tumor-associated macrophages (13, 14). The t-CD8 retain the beneficial effect already seen in the pre–rituximab era. (Table 3).
Figure 2. Associations of lymphocytes with treatment responses stratified by randomization to IFN.
The association between a fast response to rituximab and tumor T cells implies that cells already present in the microenvironment are the first to contribute to rituximab-induced lymphoma killing. However, tumor-associated T cells showed no bearing on survival. Because there are few data on any tumor-associated immune cells being predictive for survival in rituximab-treated patients, it could be speculated that rituximab is a "microenvironment-equalizer."

In the blood, b-CD3 and b-CD4 (the latter also in multivariate analysis) correlated with good responses at EV-2, after 8 doses of rituximab. The b-CD8 were associated with longer times to next treatment. Higher b-CD3 also correlated with better overall survival. The correlation between b-CD3 and overall survival was partly tied to their link with better treatment responses, but it is noteworthy that b-CD3 remained prognostic for overall survival in responders at EV-1 ($P = 0.001$) and at EV-2 ($P = 0.002$) and when multivariate adjusted to treatment response. Thus, some part of the impact of blood T cells on survival seems unrelated to treatment-associated effects. Furthermore, higher b-CD3, b-CD4, and b-CD8 correlated with low-risk FLIPI scores. Examining each FLIPI-constituting factor, all blood T-cell subsets showed strong associations with LDH but none with age or stage. This suggests that the systemic immune cells have a connection with the biology of the lymphoma even before treatment commences. The FLIPI did not predict response to rituximab, as has been previously shown (23).

Mechanisms of action of rituximab include complement-dependent cytotoxicity, direct apoptosis, and ADCC (18). CD8$^+$ cells could enhance ADCC through their production of IFN-γ (24). The maximal clinical response to rituximab may take several months, suggesting that these short-term mechanisms are not the only ones involved. A vaccinal effect of rituximab has been proposed: Rituximab-induced lysis of lymphoma cells promotes uptake and cross-presentation of lymphoma cell–derived peptides by dendritic cells, inducing their maturation, and allowing the generation of specific antilymphoma T cells (18). The vaccinal hypothesis was recently supported by the finding of follicular lymphoma idiotype–specific T cells subsequent to rituximab treatment (25). Dendritic cells would be pivotal in a vaccinal response, because not only CD4$^+$ but also CD8$^+$ cell activation requires dendritic cells (26). CD4$^+$ cells are needed for the generation of effective antilymphoma T cells (18). In summary, both CD4$^+$ and CD8$^+$ cells would be instrumental in a vaccinal antilymphoma immune response, but they would not be the only immune cells involved.

The short courses of IFN-α in the clinical trials M39035 and MLI16865 showed clear effects on treatment responses at EV-2. IFN-α has a myriad of effects, including the enhancement of the expression of MHC (major histocompatibility complex) class I proteins and the proliferation and promotion of CD8$^+$ T cells (28). An IFN-α–driven expansion of CD8$^+$ cells could explain why the addition of IFN-α had maximal therapeutic effects in patients with low CD8$^+$ cell levels. Both in tumors and in blood, the pre-treatment CD8$^+$ cell levels correlated with better outcome in patients given only rituximab but were irrelevant in
patients also receiving IFN-α. IFN-α is known to exert an antiproliferative effect on CD4+ cells, at least in vitro (29). Taken together, this would explain why high CD4/CD8 ratios correlate with better outcome in IFN-α–rituximab-treated patients. IFN-α has been suggested for use as an adjuvant to obtain antitumor vaccinal effects (18, 28). Our data are in agreement with a slow, vaccine-like effect of IFN-α, apparent at EV-2, months after the initiation of therapy. Other important effects of IFN-α are its suppression of the lymphoma-stimulating (30) and CD8+ cell-inhibiting (31) IL-4 production in CD4+ cells and its antiangiogenic action in tumors (28). Angiogenesis has been associated with poor prognosis in follicular lymphoma (32, 33).

The limitations of our study should be noted. The method used was flow cytometry, and we have previously ascertained very good agreement between flow cytometric and computerized immunohistochemistry estimations of subsets in follicular lymphoma lymph nodes (7). Flow cytometry analyzes the whole lymph node and thus cannot assess the morphologic (intrafollicular or interfollicular) distribution of the subsets. However, our previous study showed that the total numbers of CD4+ and CD8+ cells were predictive for outcome, regardless whether intrafollicular or interfollicular (7). Subsets recently reported to be important in the follicular lymphoma microenvironment, such as FOXP3-positive (3, 4, 7, 12) and programmed death 1 (PD-1)-positive (7, 11) T cells, were not known when the flow panels were constructed for this study. FOXP3+ and PD-1+ cells are immunosuppressive, mostly by inhibiting other subsets such as dendritic cells and T-helper cells (34, 35). These effects could be favorable in follicular lymphoma, at least in a watch-and-wait phase. However, in the rituximab setting, the benefits of an immune response seem evident. It can be speculated that when patients receive rituximab, FOXP3+ and PD-1+ cells will have less beneficial effects. Another potential concern in our study is the incomplete overlap of patients with tumor and blood samples. Still, the same subsets remained significant at EV-1 and EV-2 when analyzing only patients with complete flow data from blood and tumors. Finally, 23% of the patients were previously treated. However, bias from pretrial treatments are unlikely because the previous therapy was mild and mostly given years before study inclusion and it had no effect on the rituximab response or the levels or impact of the immune cells. The lymphocyte subset levels in the tumors mirrored those from our previous follicular lymphoma cohort (6), whereas those in blood were similar to what is seen in healthy subjects (36).

Our findings support the hypothesis that the impact of immune cells on outcome is dependent on treatment protocols (15). In the future, therapy might be tailored on the basis of characteristics of blood and tumor immune cells. It could be argued that some patients do not always profit from therapies with cytotoxic effects on T cells. On the contrary, some patients might benefit from chemotherapy-free treatments such as monoclonal antibodies and immunostimulating drugs (e.g., IFN-α and lenalidomide; ref. 37).

We conclude that the therapeutic effects of rituximab are augmented by tumor T cells for rapid responses. Blood T cells correlate with slower but more sustained responses. Rituximab reverses the previously unfavorable outcome associated with higher t-CD4 and affirms the favorable role of higher t-CD8. IFN-α seems to further enhance the positive impact of high CD4+ cells and compensate for low CD8+ cell levels. We propose that flow cytometric estimations of lymphocyte subpopulations in lymph nodes and blood be considered in therapeutic trials, and in the future used for choosing the most appropriate treatment for each patient.

Disclosure of Potential Conflicts of Interest

E. Kimby has had a consultant relationship with Roche and honoraria from Roche. C.H. Geisler has had a consultant relationship with Genzyme and received honoraria from Roche and received research funding from Roche and Genzyme. T. Lehtinen has received research funding from Roche. B.E. Wahlin received the Swedish Hematology Society’s Roche Grant for Lymphoproliferative Diseases. The remaining authors declare no conflicting interests.

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References


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