**Ennui or not ennui, that is the question...**

"The only horrible thing in the world is ennui. That is the one sin for which there is no forgiveness" – Oscar Wilde [1]

Before progress can be made, we must learn to distinguish between information and knowledge. For decades, clinical trials for patients with indolent non-Hodgkin’s lymphomas (NHL) were trapped in alkylating agent ennui, comparing various standard or aggressive regimens. All we learned is that there is little difference among them, none is curative, and there is a critical need for new approaches, including agents with unique mechanisms of action.

Recent clinical trials have focused on the purine analogs fludarabine and 2-chlorodeoxyadenosine (cladribine; CdA), and the adenosine deaminase inhibitor 2’-deoxycoformycin (DCF, pentostatin). The rationale for considering these drugs is, first, their mechanism of action. The indolent NHL are characterized by lymphoaccumulation, related in part, to the bcl-2 gene, which inhibits apoptosis, and which is overexpressed in 80%–90% of patients with follicular NHL and 20%–30% of diffuse NHL [2]. Both fludarabine and CdA appear to activate apoptosis of lymphoid cells [3, 4]. Second, clinical trials and anecdotal reports which have been accumulating in the literature confirm impressive activity against chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), cutaneous T-cell lymphomas, Waldenström’s macroglobulinemia, and other indolent lymphoid malignancies. Pentostatin and cladribine achieve complete remissions (CRs) in 65%–85% of patients with HCL, although whether these patients are cured requires longer follow-up [5, 6]. Fludarabine appears to be the most active agent for CLL, with responses in more than 50% of previously treated patients, including 10%–15% CRs, and more than 70% of untreated patients, with over 30% CRs [7, 8]. Recently published randomized trials demonstrated superior response rates [8, 9] and duration [9] with fludarabine compared to alkylating-agent regimens.

Several studies have shown activity for the purine analogs against indolent NHL. Fludarabine achieves responses in half of relapsed or refractory patients, including 10%–15% CRs, with responses generally lasting 12–16 months [10–15]. CRs can be achieved in about 40% of previously untreated patients [13, 14, 16], with an overall response rate of almost 70%, a median time to progression of 13.6 months [16], but with continuous relapse. CdA achieves responses in 40% of previously treated patients, including 14%–20% CRs, but these last only 3–10 months [17–20].

More than 80% of previously untreated patients respond [21, 22], but with a median duration of response of only 10 months in one series [21], with half the patients already relapsed by 15 months in the other [22].

In this issue, Betticher et al. [23] report a carefully conducted study of 37 patients, with a CR rate of 14%, less than half that in the other series, but a comparable overall response rate (84%) and duration of response (10 vs. 15.7 months), also with no plateau on the survival curve. Of note is that almost a third of patients could not complete the planned courses of therapy, half related to toxicity. Their failure to detect a correlation between response duration and bcl-2 expression most likely reflects the small sample size. The authors felt that the duration of responses was no longer than with alkylating agents therapy and, therefore, they considered their results disappointing.

To place this information into perspective, it is instructive to consider the history of other purine analogues. The early experience with 6-mercaptopurine in acute lymphoblastic leukemia noted approximately 20% responses; but, this drug was valuable in combination with other agents [24]. As a medical student, I was intrigued by a seminal paper from the Cancer and Leukemia Group B, describing a new purine analogue, cytosine arabinoside, in the treatment of adult acute myeloid leukemia. CR rates were higher than were formerly achievable; nevertheless, in previously untreated patients, the median survival was less than 10 weeks, with no plateau on the curve [25]. My professors considered the drug a failure. However, the subsequent addition of anthracyclines resulted in complete remissions in more than 50% of patients, with 40% of these being cured, and cytarabine is considered a critical drug in the treatment of this disease [26].

In fact, response rates with purine analogs in indolent NHL are at least comparable to alkylating agents when similar measures of response are used, and these drugs should be considered components of standard treatment. Which analogue is the winner cannot be answered with certainty from the published information [27]. Because of the small sample sizes, and patient heterogeneity, it is equally difficult to compare results between the drugs as among studies with the same agent.

Fortunately, interest in directly comparing these drugs was short-lived [27]. Such information is irrelevant since more effective, potentially curative strategies are needed. The greater promise of these purine analogs lies in combinations developed with scientific rationale. For example, fludarabine and CdA interfere
with the DNA repair following exposure of cells to radiation, alkylating agents and topoisomerase II inhibitors. The combination of fludarabine and the TP II inhibitor, mitoxantrone results in CRs in more than 40% of previously treated patients, with response rates as high as 94% [28, 29]. The median failure-free survival was 21 months for CRs and 9 months for partial responders. The Southwest Oncology Group has completed a confirmatory trial, and yet another has been published [30]. This regimen is being pursued as frontline treatment. A similar combination was subsequently developed with CdA [31]. Combining cyclophosphamide and fludarabine achieved a 100% response rate including 89% complete remissions in 27 previously untreated patients [32]. Longer follow-up is needed to assess the durability of the responses.

A variety of new agents are in clinical trials; paclitaxel and fenretinide (4-HPR) agents by applying our rapidly increasing understanding of the knowledge hiding beyond the data will we develop NHL, which is, perhaps, greater when combined with bcl-2 apoptosis or deregulate bcl-2 [33, 34], topoisomerase I inhibitors, and the protein kinase C modulators bryostatin and UCN-01. Although these may have limited single agent activity, their potential for synergistic combinations is being explored.

Of particular interest are new biological agents, including monoclonal antibodies [35], radioimmunoconjugates [36, 37], antisense compounds, and others which target specific genes, such as bcl-2 and p53.

The purine analogs have major activity in indolent NHL, which is, perhaps, greater when combined with mitoxantrone. Additional confirmatory trials would only prolong an era of purine analogue ennui. Clinical research should focus on optimizing the use of new agents by applying our rapidly increasing understanding of immunology and biology. Only when we acquire the knowledge hiding beyond the data will we develop the innovative strategies that will cure the indolent lymphoid malignancies.

References