Gaynor and Fisher provide a literature review and analysis of the significance of dose intensity in determining treatment outcome in patients with intermediate-grade non-Hodgkin's lymphoma (NHL). Since most of the patients in the studies reviewed had diffuse large-cell lymphoma or its variants, that is the term that will be used in the remainder of this commentary. In their analysis, Gaynor and Fisher reach the conclusion that in the dose range tolerable without extraordinary supportive measures, increasing dose intensity has no demonstrable benefit.

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**Definition of Dose Intensity**
When one considers the issue of the dose of chemotherapeutic agents and its impact on treatment outcome, it is important to be certain that the author and reader are using the same definitions. When speaking of dose intensity--i.e., dose per unit time, usually milligrams per square meter per week--the value of dose intensity could be documented by showing an improved outcome with higher dose intensity or a worse outcome with lower dose intensity. It would be possible to find one outcome and not the other. "Standard" dose intensity with a particular regimen is the dose and schedule that has been found to be tolerable through the trial and error of clinical studies. The "standard" dose level achieves a certain treatment outcome without the level of toxicity that clinicians and patients would find unacceptable.

As Gaynor and Fisher point out, a significant decrease in dose intensity below that considered "standard" is often associated with a poorer treatment outcome. They present examples in patients treated with diffuse large-cell lymphoma [1]. This has also been found to be the case in other malignancies. For example, the Cancer and Leukemia Group B showed that reduced doses of adjuvant chemotherapy in breast cancer led to poorer treatment results [2]. Much of the article by Gaynor and Fisher is spent illustrating the facts that:

1. It is difficult to produce a significant increase in dose intensity beyond that considered standard because of toxicity.
2. The 20% to 30% increase in dose intensity that can be achieved does not seem to improve treatment outcome in patients with diffuse large-cell lymphoma.

The authors support this argument with retrospective analyses of clinical trials and prospective randomized trials. These results suggest that the shape of the dose-response curve must have a deflection around the dose level that we consider "standard" (Figure 1). The dose-response curve must be steeper below the "standard" dose intensity than it is above the "standard" level.

**Other Variables Besides Dose Intensity May Be Important**
Another issue that needs to be considered in determining the effect of dose in cancer therapy is that dose intensity may be only one of several important variables. Others include the peak dose achieved and the total dose administered. e, i.e., intuitively, the highest possible dose per unit time may seem to be important, it is possible that the best way to overcome potential treatment resistance would be to overwhelm resistance mechanisms with a very high peak level of the drug(s). This, of course, is the approach that is taken in bone marrow transplantation. It is also possible that the total amount of drug administered, rather than the rate at which it is administered, may be an important issue. In contrast to dose intensity, which has received
considerable attention (as highlighted by Gaynor and Fisher), and high peak dose levels, as utilized in bone marrow transplantation, the impact of varying the total dose administered has been studied less often. Since it became apparent that in curable malignancies, cure can usually be achieved with fairly brief therapy, most efforts have been aimed at minimizing the total doses administered to avoid long-term toxicity.

**Results May Change With Very Long Follow-Up**

One other issue that needs to be considered in interpreting the studies reviewed by Gaynor and Fisher is the potential importance of very long-term follow-up. If the results of the studies that they review were to change with very long follow-up, that would not be a unique event in oncology. For example, in studies of very-high-dose therapy associated with bone marrow transplantation, at least three studies were initially reported to be negative, but the benefits of high-dose therapy became apparent on very long follow-up [3-5].

In this regard, one of the studies comparing CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) to a six-drug combination chemotherapy regimen in diffuse large-cell lymphoma, performed by the Australia and New Zealand Lymphoma Study Group, was originally negative, in that neither treatment demonstrated an advantage. However, with very long follow-up, the six-drug regimen appears to be superior (MM Wolf, personal communication, 1994; and reference 6).

**Do Very High Single Doses Improve Outcome?**

Even if increasing dose intensity, when defined as milligrams per square meter per week, does not appear to provide an avenue to improving treatment outcome for patients with diffuse large-cell lymphoma, the approach of very-high-dose single treatments (ie, autologous bone marrow transplantation) does seem to provide an advantage in certain situations. The recently completed PARMA study demonstrated that, for patients with relapsed but chemotherapy-sensitive diffuse large-cell lymphoma, one pulse of very high doses of carmustine (BiCNU), etoposide (VePesid), cytarabine, and cyclophosphamide (Cytoxan, Neosar) was superior to a more standard approach of multiple courses of dexamethasone, high-dose cytarabine, and cisplatin (Platinol) [5].

Obviously, this raises the issue of whether or not very-high-dose pulses of chemotherapy with autologous bone marrow transplantation might be able to improve primary treatment outcome for patients with diffuse large-cell lymphoma. If this approach were to be adopted, there are still multiple treatment strategies available. The high-dose treatment could be an early, integral part of the treatment regimen, it could be reserved for patients who are identified to be at high risk because of slow response or other characteristics, or it could be used as an adjuvant therapy in complete responders. All of these approaches are being tested, and several have been incorporated into prospective randomized trials. Results to date have been optimistic in some cases [7,8] and pessimistic in others [9].

At present, this is the most hopeful, easily tested approach to improving outcome in younger patients with diffuse large-cell lymphoma. The results of ongoing trials should provide insight and direction for clinicians regarding the value of this approach.

**References:**


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