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# The Treatment of Cancer Patients with Human Lymphoblastoid Interferon

## A Comparison of Two Routes of Administration

James A. Knost[1], Stephen A. Sherwin[1], Paul G. Abrams[1], Jeffrey J. Ochs[1], Kenneth A. Foon[1], Roxanne Williams[1], Richard Tuttle[2], and Robert K. Oldham[1]

[1] Biological Response Modifiers Program, Division of Cancer Treatment, National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD 21701

[2] Burroughs-Wellcome Co., Research Triangle Park, NC 27709, USA

***Summary.*** *Highly purified human lymphoblastoid interferon (HLBI) derived from virus-stimulated Namalwa cells was administered by 6-h IV infusion or IM injection to 40 patients with a variety of disseminated malignancies refractory to standard therapy. Each patient received doses escalating from 0.1 to 50 × $10^6$ U for up to 5 weeks. Extensive monitoring for clinical effect, toxicity, and pharmacokinetics has revealed higher peak serum interferon levels and somewhat more pronounced systemic toxicity for the IV than for the IM route of administration. Objective evidence of tumor regression was observed in two patients receiving HLBI IV.*

### Introduction

Alpha interferons, including those produced by normal leukocytes and by lymphoblastoid cell lines, are being widely studied for their possible therapeutic efficacy in man and have been shown to have some antitumor activity in lymphoma, myeloma, breast cancer, melanoma and other malignancies [7–11, 13, 14, 16]. Human lymphoblastoid interferon (HLBI) is a mixture of alpha interferons induced by Sendai virus in large-scale cultures of Namalwa, a B cell line. Previous studies with this type of interferon have indicated that it can be administered safely by the IM and IV routes and that it has some antitumor activity in patients with various hematologic and nonhematologic malignancies [17, 18, 20]. These preliminary studies suggested some unexpected differences in the tolerance of HLBI when given by these two routes of administration, including a reportedly lower maximum tolerated dose (MTD) for the IM route [17] than for the IV route [19]. We now report the results of an escalating-dose phase I trial of HLBI in which two groups of patients were treated with the same schedule by the IM or the IV route. These different routes of administration have been compared with respect to clinical effect, toxicity, and levels of serum interferon activity.

### Materials and Methods

The human lymphoblastoid interferon (HLBI) used in these studies was prepared from Sendai virus-induced human Namalwa cells and purified using an anti-interferon antibody affinity system produced by Wellcome Research Laboratories, Beckenham, England. The specific activity of HLBI is 1–2 × $10^8$ U/mg and the purity is approximately 90%. HLBI has been shown to be a mixture of alpha interferons composed of at least eight molecular species by gel analysis [5].

In this study HLBI was administered by 6-h IV infusions or by IM injection, daily for 5 days (Monday through Friday) over 5 successive weeks. The daily dose was escalated weekly in each patient according to the following schedule: 0.1 × $10^6$, 1 × $10^6$, 10 × $10^6$, 30 × $10^6$, and 50 × $10^6$. The study of HLBI given by the IV route of administration was concluded prior to initiation of the study with the IM route. The patients in the IM group did not receive treatment with 50 × $10^6$ U due to unacceptable hematologic and hepatic toxicity in the IV group at this dosage level. In this study, unacceptable hematologic toxicity was defined as a granulocyte count ≤ 500/$mm^3$ or a platelet count ≤ 50,000/$mm^3$, and unacceptable hepatic toxicity was defined as SGOT > 150 IU/ml.

All treated patients had histologically confirmed advanced malignant disease refractory to standard treatment with radiotherapy and/or chemotherapy. Informed consent was obtained prior to participation in the study. Complete blood counts, routine clinical chemistry values, and baseline serum interferon activity were determined prior to HLBI administration. These measurements were repeated biweekly during the treatment period and for up to 2 weeks after the last dose. To assess antitumor effect appropriate radiologic studies of tumor lesions were obtained before and after therapy with HLBI. Patients showing objective evidence of tumor response were eligible to continue therapy with HLBI with weekly injections of 10 × $10^6$ U of HLBI. Responses were graded according to the following criteria: partial response, a greater than 50% decrease in the product of the longest perpendicular diameters of all measurable lesions without the appearance of new lesions; stable disease, no decrease in tumor size that would qualify as a partial response and no new lesions or enlargement of measured lesions which would qualify as progression; progressive disease, a 25% or greater increase in the product of the longest perpendicular diameters of any measured lesion or the appearance of new lesions during the treatment period.

Full pharmacokinetic profiles were obtained on all patients treated on day 1 of each treatment cycle. Serum interferon activity determinations were taken at 0, 1, 2, 4, 6, 7, 8, 10, 12, and 24 h after the HLBI injection or after the start of the HLBI infusion. For selected patients treated at 50 × $10^6$ U these same measurements were determined on each of the 5 days of the treatment cycle. Interferon activity was measured in a bioassay as judged by inhibition of plaque formation by vesicular

*Reprint requests should be addressed to* R. K. Oldham, MD, Building 567, NCI-Frederick Cancer Research Facility

stomatitis virus-mediated lysis of human fibroblast cells. One unit of interferon activity was defined as the reciprocal of the serum dilution resulting in 50% inhibition of plaque formation with reference to National Institutes of Health Standard GO23901-527.

## Results

Forty patients were entered in the study including both the IV (29 patients) and IM (11 patients) groups. As shown in Table 1, of 29 IV patients four were removed in the first week because of medical problems unrelated to HLBI toxicity, and five additional patients had progressive disease while receiving therapy. Twenty patients were evaluable for toxicity at dosages of $30 \times 10^6$ U IV for 5 days. An additional 13 patients were evaluable at $50 \times 10^6$ U IV. When six of 13 patients demonstrated unacceptable hematologic or hepatic toxicity at $50 \times 10^6$ U IV as defined by the protocol, no further patients were treated at that dose. One of the 11 IM patients was removed from the study due to tumor progression and the remaining 10 patients were evaluable for toxicity at the $30 \times 10^6$ U dose level.

### *Toxicity*

The most common side-effects seen with both the IV and the IM route of administration were similar to those observed with other alpha interferon preparations [17, 18, 20] and included fever, chills, fatigue, anorexia, and nausea and vomiting. As shown in Table 2, these effects were dose-dependent, occurring more frequently as the dose was escalated, and almost uniformly at the $50 \times 10^6$ U level.

Those patients entered on the IV schedule demonstrated a maximum temperature of 104° F, with the majority of the patients having temperatures of 101–103° F at the $10-50 \times 10^6$ U doses. Pretreatment with acetaminophen blunted but did not abolish the fever. Tachyphylaxis to the febrile response was demonstrated, with less temperature elevation being observed on days 2–5 of each treatment cycle. Weight loss of 5–10 lb was recorded in all of the patients. Of 13 patients at the $50 \times 10^6$ U dose, nine required supplemental IV fluids because of negative fluid balance that was thought to be secondary to poor oral intake and increased insensible loss from daily fevers. While fatigue was prominent in all the patients at the $50 \times 10^6$ U dose and most of the patients at the $30 \times 10^6$ U dose, only one patient was removed from the study (at the $30 \times 10^6$ U dose) because of profound fatigue. All patients were ambulatory at the start of therapy. This level of function was maintained in most patients until the $50 \times 10^6$ U dose, at which point nearly all patients remained in bed for > 50% of the time (Karnofsky performance < 50%). One patient had mental confusion at the $50 \times 10^6$ U dose, which cleared within 36 h of the discontinuation of interferon therapy. In addition, four patients treated at this dose had orthostatic hypotension in the absence of clinically apparent hypovolemia and despite adequate hydration. All four patients experienced dizziness and one patient had a syncopal episode.

The dose-limiting toxicities for the IV route of administration are shown in Table 3. Two of 20 patients given $30 \times 10^6$ U IV and six of 13 receiving $50 \times 10^6$ U IV had unacceptable hematologic or hepatic toxicities as defined in the protocol (granulocyte count < 500/mm$^3$, platelet count < 50,000/mm$^3$ or SGOT > 150 IU/ml). Absolute granulocyte counts of < 500/mm$^3$ were seen in three patients (one at $30 \times 10^6$ and two at $50 \times 10^6$). No septic episodes occurred and leukocyte recovery was seen in 24 h with a return to baseline in 72 h. Thrombocytopenia of 40,000–50,000/mm$^3$ was seen in two patients at $50 \times 10^6$ U, but no spontaneous or uncontrolled bleeding occurred. A significant rise in the platelet count from the nadir took up to 1 week. A gradual rise in the SGOT to > 150 IU/ml was noted in one patient at $30 \times 10^6$ U and three patients at the $50 \times 10^6$ U dose. These elevated levels began to decrease 24 h after HLBI was discontinued, with full recovery seen in 1 week. Based on the occurrence of unacceptable toxicity in six of 13 patients treated at $50 \times 10^6$ U, we defined $30 \times 10^6$ U IV daily for 5 days as the MTD with this treatment regimen. However, the study design employed with dose escalation in individual patients prevents a precise determination of MTD due to the possibility of cumulative toxicity.

As shown in Table 2, side-effects in the IM group tended to parallel those in the IV group. Temperatures of 101–103° F and tachyphylaxis to fever were again noted. Chills, fatigue,

**Table 1.** Patient status

| | | |
|---|---|---|
| IV | Entered on study | 29 |
| | Removed due to progression | 5 |
| | Removed due to medical problems unrelated to HLBI | 4 |
| | Evaluable for toxicity at $30 \times 10^6$ U | 20 |
| | Evaluable for toxicity at $50 \times 10^6$ U[a] | 13 |
| IM | Entered on study | 11 |
| | Removed due to progression | 1 |
| | Evaluable for toxicity at $30 \times 10^6$ U | 10 |

[a] This dosage level was closed after 6 of 13 patients experienced unacceptable toxicity

**Table 2.** Systemic toxicity following HLBI administration[a]

| Route | HLBI ($\times 10^6$ U) | Fever | Chills | Fatigue | Anorexia | Nausea | Vomiting |
|---|---|---|---|---|---|---|---|
| IV | 0.1 | 6/25 | 0/25 | 1/25 | 1/25 | 0/25 | 0/25 |
| | 1.0 | 15/25 | 2/25 | 1/25 | 2/25 | 0/25 | 0/25 |
| | 10.0 | 19/21 | 16/21 | 10/21 | 5/21 | 3/21 | 3/21 |
| | 30.0 | 20/20 | 20/20 | 14/20 | 11/20 | 6/20 | 3/20 |
| | 50.0 | 13/13 | 12/13 | 12/13 | 13/13 | 8/13 | 2/13 |
| IM | 0.1 | 2/11 | 0/11 | 1/11 | 0/11 | 0/11 | 0/11 |
| | 1.0 | 3/11 | 1/11 | 4/11 | 2/11 | 0/11 | 0/11 |
| | 10.0 | 6/11 | 4/11 | 8/11 | 4/11 | 4/11 | 1/11 |
| | 30.0 | 10/10 | 8/10 | 11/10 | 7/10 | 4/10 | 2/10 |

[a] Data are expressed as number of patients with toxicity/number of patients evaluable for toxicity at that dose level

anorexia, weight loss, nausea, and vomiting occurred with a frequency similar to that in the IV group, but were generally less intense. Side-effects were dose-dependent, being most frequent at the 30 × $10^6$ U dose. No episodes of mental confusion were noted with IM administration up to doses of 30 × $10^6$ U. Table 3 shows the dose-limiting toxicities for the IM group of patients. One patient had a single granulocyte count of < 500/$mm^3$ on the third day of treatment with 30 × $10^6$ U. However, only one patient was removed from the study because of unacceptable hematologic toxicity, and this was for a platelet count of 40,000/$mm^3$.

*Antitumor Effect*

Of 40 patients, 36 were evaluable for antitumor response to therapy (25 IV and 11 IM). Four patients receiving less than 1 week of therapy IV are excluded from consideration. As shown in Table 4, 24 patients had stable disease (16 IV and 8 IM) and 10 had progression (7 IV and 3 IM). Five of the patients with progressive disease were removed during the study for this reason.

Two patients receiving HLBI IV showed a partial response or a > 50% reduction in the products of two perpendicular diameters lasting a minimum of 4 weeks. The first patient was a 44-year-old male with an anaplastic carcinoma of undetermined origin. The mass presented in the right groin and initially responded to radiotherapy. Within weeks after the end of radiotherapy a new mass appeared in the right gluteal area. Biopsy of this mass just prior to initiation of HLBI therapy showed recurrent anaplastic carcinoma. At the outset of therapy this mass and a left retroperitoneal mass were evaluable. Objective evidence of tumor regression became apparent during the second week of therapy (1.0 × $10^6$ U dose) and by the end of therapy there was a > 50% reduction in both masses as judged by physical examination and CT scanning of the abdomen. The patient then received maintenance therapy consisting of 10 × $10^6$ U IM weekly. A stable partial response was maintained for 4 months, at which time HLBI was discontinued and radiotherapy to the only two known sites of disease was administered. The patient continues to have a stable partial response 9 months after the initiation of HLBI therapy. The second patient was a 56-year-old female with nodular poorly differentiated lymphocytic lymphoma. The patient had received extensive prior radio- and chemotherapy. The patient's evaluable disease was lymphadenopathy in the neck, supraclavicular area, and retropertioneum. Lymph node regression was first noted during the second week of therapy (1.0 × $10^6$ U dose) and after 3½ weeks of therapy there was a partial response as determined by physical examination. The HLBI was discontinued at this time because of thrombocytopenia with a platelet count of 40,000/$mm^3$. The thrombocytopenia persisted for 2 weeks, after which maintenance therapy with HLBI at 10 × $10^6$ U IM weekly was administered. This response lasted a total of 3 months. In the group of 11 patients receiving HLBI IM no objective partial responses were noted.

**Table 3.** Dose-limiting toxicity following HLBI treatment[a]

| Route | HLBI (× $10^6$ U) | Granulocytes (< 500/$mm^3$) | Platelets (< 50,000/ $mm^3$) | SGOT (> 150 IU/ml) |
|---|---|---|---|---|
| IV | 0.1 | 0/25 | 0/25 | 0/25 |
| | 1.0 | 0/25 | 0/25 | 0/25 |
| | 10.0 | 0/21 | 0/21 | 0/21 |
| | 30.0 | 1/20 | 0/20 | 1/20 |
| | 50.0 | 2/13 | 2/13 | 3/13 |
| IM | 0.1 | 0/11 | 0/11 | 0/11 |
| | 1.0 | 0/11 | 0/11 | 0/11 |
| | 10.0 | 0/11 | 0/11 | 0/11 |
| | 30.0 | 1/10 | 1/10 | 0/10 |

[a] Data are expressed as number of patients with toxicity/number of patients evaluable for toxicity at that dose level

**Table 4.** Antitumor response

| | | |
|---|---|---|
| IV | Patients entered | 29 |
| | Patients evaluable for response | 25[a] |
| | Partial response | 2 |
| | Stable disease | 16 |
| | Progression | 7 |
| IM | Patients entered | 11 |
| | Patients evaluable for response | 11 |
| | Partial response | 0 |
| | Stable disease | 8 |
| | Progression | 3 |

[a] This excludes four patients who received less than 1 week of HLBI therapy

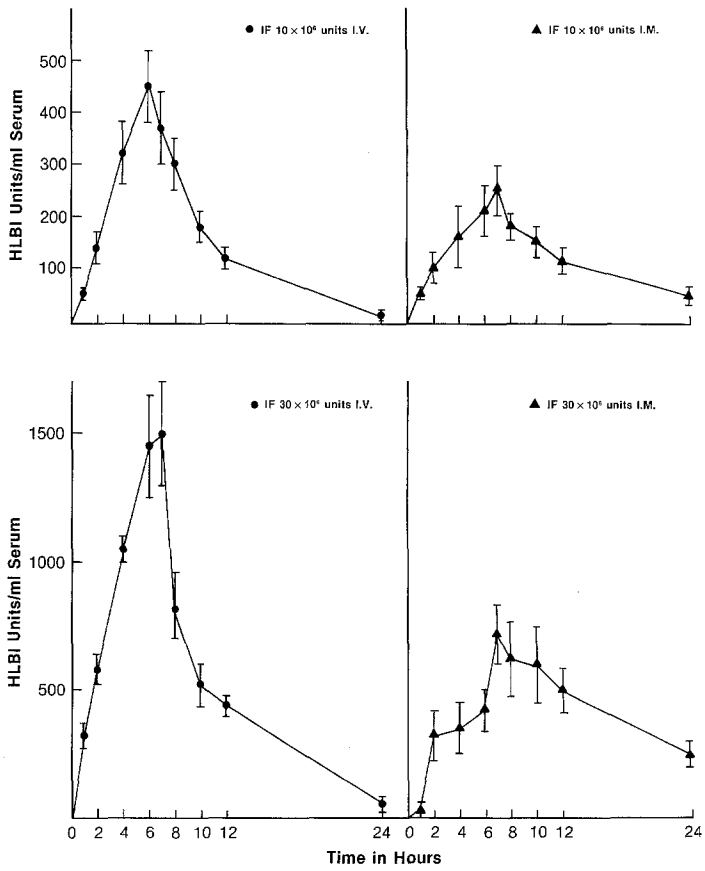


**Fig. 1.** Serum interferon activity following HLBI treatment by 6-h IV infusion or IM injection at doses of 10 × $10^6$ and 30 × $10^6$ U. Each *point* represents the mean ± SE

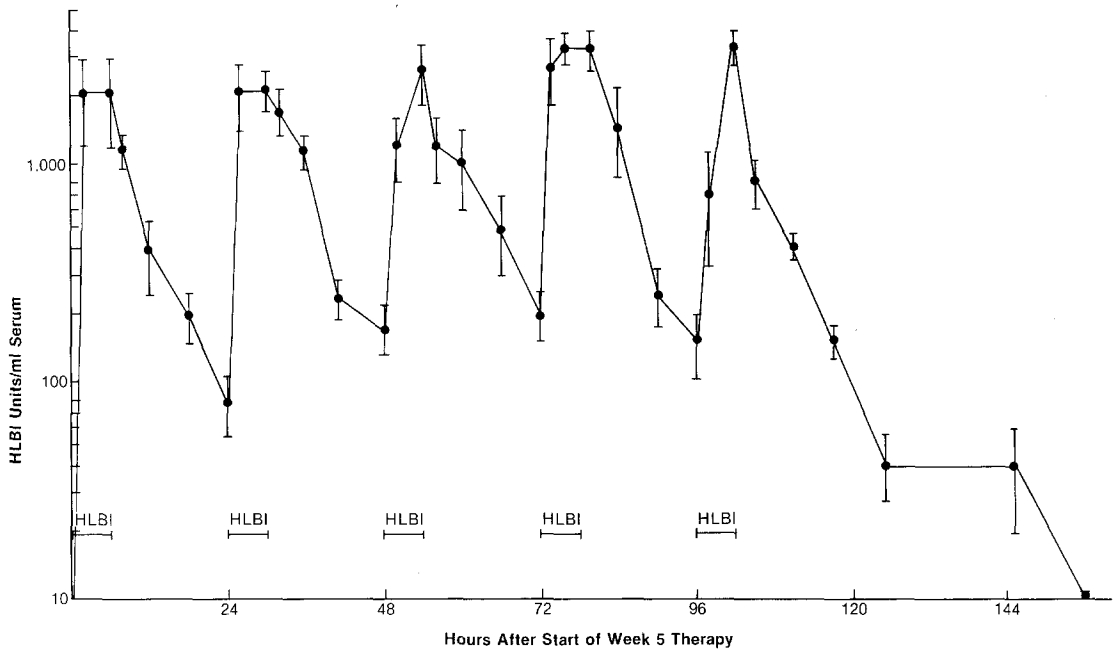


**Fig. 2.** Serum interferon activity measured during the 5 days of therapy with HLBI at a dose of $50 \times 10^6$. Patients received five daily 6-h infusions as indicated by the *solid horizontal bar*. Each *point* represents the mean value ± SE

*Pharmacokinetics*

Patients were monitored extensively for serum interferon activity following both IV and IM administration of HLBI. As shown in Fig. 1, serum interferon activity following 6-h IV infusions of 10 and $30 \times 10^6$ U gives higher peak levels (means + standard error = 450 ± 70 U and 1,500 ± 200 U/ml, respectively) than the IM dose (means ± standard error = 250 ± 60 U and 710 ± 130 U/ml, respectively). The peak serum level occurred at approximately 6–7 h from the start of therapy with both routes of administration. Interestingly, the 12-h levels at 10 and $30 \times 10^6$ U were approximately the same for both routes, whereas the 24-h levels were somewhat higher following IM injection. This suggests a potentially greater steady-state accumulation of drug when it is given by the IM route. However, repeated daily 6-h IV infusions of HLBI can also result in significant steady-state levels. Figure 2 shows serum interferon activity at various time points for the patients treated at $50 \times 10^6$ U daily for 5 days. Steady-state interferon levels in excess of 100 U/ml are achieved with this regimen. Moreover, there appears to be an upward trend, although not statistically significant, in both peak and steady-state interferon levels.

## Discussion

In this study 40 patients received HLBI by 6-h IV infusion or IM injection in escalating doses over a 4–5 week period. Comparisons were made of clinical effect, toxicity, and pharmacokinetics for these two routes of administration. It was felt that the MTD for both routes of administration was $30 \times 10^6$ U daily × 5 days. The next dose ($50 \times 10^6$ U) gave unacceptable toxicity IV, with six of 13 patients having significant depression of granulocyte or platelet count, and/or elevation in hepatic transaminase level. Rohatiner et al., in a study employing 5-day continuous IV infusions of HLBI, felt that the MTD for this regimen was $50 \times 10^6$ U/m$^2$ daily for 5 days [19]. Laszlo et al. conducted a study of HLBI given IM with a 3 × weekly schedule in which each patient was given escalating dosages with $5 \times 10^6$ increments until the MTD was defined. In this study unacceptable fatigue as assessed by the patient was an end-point for toxicity. The MTD was felt to be $15 \times 10^6$ U/m$^2$ IM 3× weekly [10]. Sarna et al. recently reported a phase I study in which HLBI was given IM twice daily for 14 days. At each level three new patients were entered. The MTD was felt to be approximately $30 \times 10^6$ U twice daily [21]. The MTD defined in our study for both the IM and IV routes as $30 \times 10^6$ U daily × 5 days falls between that reported by the latter two investigators. However, it should be noted that our study design of dose escalation within individual patients precludes a precise determination of MTD, since some cumulative toxicity may have occurred in our patients.

The toxicity seen in this study is similar in most respects to that reported for other alpha interferons, and includes fever, chills, fatigue, anorexia, and nausea and vomiting [1, 16, 17, 22]. As previously reported for lymphoblastoid interferon, the side-effects appear to be dose-dependent, being unusual below $10 \times 10^6$ U and increasing with doses of 10, 30, and $50 \times 10^6$ U daily. It appears that granulocytopenia, thrombocytopenia, and liver dysfunction (transaminase elevation) are the objective dose-limiting toxicities. The rapid recovery of granulocytes and transaminase elevations have also been observed by other investigators [16, 17, 22]. It has been observed that interferon exerts an in vitro suppression of colony growth from stem cells [6, 12, 15]. However, the prompt rise in the leukocyte count within 24 h suggests that HBLI is not toxic in vivo to stem cells in the myeloid series, whereas the longer recovery for platelets suggests that there may be such toxicity in the megakaryocyte series.

The pharmacokinetic data gathered in this study show that high levels of serum interferon activity can be obtained by the IV and, to a lesser extent, the IM route of administration of HBLI. Levels in excess of 50 U/ml serum can be maintained for 24 h when HLBI is given by either route in dosages $> 10 \times 10^6$ U.

Other investigators have noted similar pharmacokinetic parameters for alpha interferons. Cantell and Pyhälä reported on the pharmacology of IM and IV nonrecombinant leukocyte interferon [4]. They concluded that the IV route gave superior peak levels, but both the time to peak values and the rate of clearance were the same for both routes. Greenberg also noted a peak serum interferon value when $3 \times 10^6$ U of alpha interferon were given IM [6]. At this dose, detectable levels were noted at 24 h. Sherwin et al. reported peak interferon values at 6 h and sustained 24-h levels in a fixed multiple-dose recombinant leukocyte interferon study [22]. The lower absolute peak value and sustained levels of IM as compared to IV HLBI in our study could be explained by the prolonged release of glycoproteins from IM sites, since carbohydrate residues are known to delay glycoprotein release. The removel of these groups from lymphoblastoid interferon is known to markedly alter its clearance in animals [2, 3].

The patients on this study were also monitored extensively at each dose level for the in vivo immunologic effect of HLBI with assays for natural killer (NK) cell-mediated cytotoxicity, monocyte function as measured in a growth inhibition assay, and lymphoproliferative response following exposure to mitogen. The results of these studies will be reported in detail elsewhere (A. E. Maluish et al. 1983, manuscript in preparation). There was no significant difference in in vivo immunologic effect between the IM and IV routes of administration and no clear dose-response effect either.

In conclusion, our study has demonstrated that it is feasible to administer HBLI in escalating doses of up to $30 \times 10^6$ U daily $\times$ 5 days by either the IV or the IM route. The IV route of administration is associated with somewhat higher peak serum levels and more pronounced systemic toxicity. Objective tumor responses were seen when HLBI was given IV to one patient with anaplastic carcinoma and one patient with nodular poorly differentiated lymphocytic lymphoma. Determination of the therapeutic role of HLBI in these and other specific malignancies must await the results of phase II efficacy trials now in progress.

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