

Review article

# The role of low-dose total body irradiation in treatment of non-Hodgkin's lymphoma: a new look at an old method

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## Abstract

The use of low-dose total body irradiation (LTBI) in treatment of lymphomatous malignancies dates back to the 1920s. The usual practice was to give very low individual TBI fraction sizes (0.1–0.25 Gy) several times a week to a total dose of 1.5–2 Gy. Despite this very low total dose, LTBI could induce long term remissions and was always as effective as the chemotherapy to which it was compared. In modern radiotherapy, LTBI is still a valid option in treatment of chronic lymphocytic leukaemia (CLL) and the advanced stages of indolent low-grade non-Hodgkin's lymphoma (NHL). Its use in the early stages of low-grade NHL is under investigation in a large multi-institutional trial. The efficacy of LTBI is believed to stem from three mechanisms, namely; immune-enhancement, induction of apoptosis, and the intrinsic hypersensitivity to low-radiation doses demonstrated in many cell lines and tumour systems. Thus, LTBI seems to provide 'alternative' mechanisms of action against cancer cells. This should encourage researchers to explore strategies that integrate LTBI in new and innovative experimental treatment protocols that explore the possible synergism between LTBI and chemotherapy, biological response modifiers and/or immunotherapy. The increased incidence of secondary leukaemia that occurs when LTBI is combined with alkylating agents and/or total lymphoid irradiation should be kept in mind when designing such protocols as it may limit the use of LTBI in highly curable diseases and young patients in whom long survival is expected. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Low dose irradiation; Whole body irradiation; Non-Hodgkin's lymphoma

## 1. Background and introduction

It is interesting to note that the first therapeutic total body irradiation (TBI) in the 1920s, was, by our current definition of dose delivery, a low-dose irradiation. The patients were given a fraction of the 'erythema dose' twice weekly for few weeks until there was an appreciable fall in the peripheral counts of the white cells and/or platelets [16,37]. With this type of treatment an estimated total dose of 3 Gy was rarely exceeded when given as, for example, 0.1 Gy/fraction. The results were encouraging and the complications that were in the form of bleeding and infections could have been attributed to the disease as well as to the treatment [44].

After the discovery of the first chemotherapeutic agents in the 1950s, the interest in low-dose total body irradiation (LTBI) was diminished since these agents were regarded as a more feasible and, logical option for treatment of disseminated malignancies. Then, starting from the late 1960s and early 1970s, the use of LTBI in treatment of chronic lymphocytic leukaemia (CLL) and NHL was revived, thanks to the work of Johnson [22–29] and Qasim [40,41].

The published results were very promising, but yet again, the clinical research in LTBI was almost abandoned in the 1980s and 1990s in favour of the more aggressive anthracyclin-containing regimens of combination chemotherapy.

## 2. Results of low-dose total body irradiation

Typically, LTBI was used in treatment of advanced stage NHL and the standard schedule consisted of giving 0.1–0.25 Gy per fraction, 1–5 times a week to a total dose of 1.5–2 Gy. Table 1 shows the results of selected studies that span a period of 23 years. When used ab initio, LTBI gave a high overall response rate that ranged from 70 to 90% for nodular lymphomas and from 50 to 80% for Diffuse types [17,18,35].

Though the total dose of TBI varied between reports from 1 to 3 Gy, there seems to be no difference in the outcome between the various dose levels. Only one study has identified TBI dose (in multivariate analysis), as one of the indicators of survival and recurrence free survival (RFS) [36].

Giving TBI over a short course of 10 daily fractions over

Table 1  
Selected studies that span a period of 23 years and reporting the use of LTBI as a primary treatment of NHL<sup>a</sup>

Reference (year)	NHL histological subtype	Number of (evaluable) patients	NHL Stage	LTBI Total dose (Gy)	Additional treatment	LTBI-induced complete remission (%)	5-year overall survival (%)
Johnson [23] (1975)	Well diff. <sup>b</sup>	9	III-IV	1.0-1.5	Total nodal irradiation (8 patients)	100	85
Chaffey et al. [5] (1977)	PD, Nodular <sup>b</sup>	30	III-IV	1.5	Involved field (residuals)	61.5	69
	PD, Diffuse <sup>b</sup>	18				64	51
	Nodular <sup>b</sup>	36				80 (all patients)	80
Carabell et al. [4] (1979)	Diffuse <sup>b</sup>	15	III-IV	1.5	Involved field (24 patients)	Not mentioned	45
	Nodular	43	III-IV	1.5	Involved field (24 patients)	Not mentioned	65
Dobbs et al. [12] (1981)	Diffuse <sup>b</sup>	15	III-IV (13 in relapse)	1.5	No	63.5	42
	Nodular <sup>b</sup>	22					32
Lybeert et al. [33] (1987)	Diffuse <sup>b</sup>	15	II-IV	1.8-2.2	Involved field to residuals (3 patients)	40	8
	Favourable <sup>c</sup>	25				Not mentioned	48
Mendenhall et al. [36] (1989)	Unfavourable <sup>c</sup>	20	II-IV	1.5-3	Involved field to residuals and bulky (16 patients)	74	15
	Favourable <sup>c</sup>	27				41 (all patients)	
Richaud et al. [43] (1998)	Unfavourable <sup>c</sup>	17	I-II	1.5	Involved field (all patients)	35	80 (crude survival)
	Low grade, follicular <sup>c</sup>	26				92	

<sup>a</sup> The data of patients treated with LTBI when in relapse were extracted and omitted from the table (whenever possible). When the 5-year survival figure was not explicitly stated in the text of the original article the number was extracted from graphs. The papers mentioned in the table are only a sample representing 'typical' results. The selection of the articles to be in the table was based on the number of patients and publication date.

<sup>b</sup> According to Rappaport classification.

<sup>c</sup> According to the Working formulation.

12 days or as a long protracted course of a few weeks did not seem to affect the clinical outcome [12]. As seen in Table 1, adding a localized boost field of irradiation to sites of bulky or residual disease was a common practice, although its value was never studied in a randomized trial. Combining LTBI with total nodal irradiation did not give superior results but seemed to have caused high incidence of secondary leukaemia [23].

The problem of changing the histopathological classification and nomenclature of NHL is but one of the many difficulties that confound evaluating and critically appraise the results of LTBI from old literature. Other problems such as the retrospective nature of most of the studies, the small number of patients, the non-uniformity of treatment techniques and dose-fractionation schedules, the inclusion of heterogeneous groups of pre-treated and de novo patients, and the lack of detailed criteria of response would all affect the confidence by which one could draw solid conclusions. The most recent studies, however, seem to suggest that LTBI is as effective now as it was 20 years ago. In 1998, Richaud et al. treated 26 patients with previously untreated localized (stage I–II) low-grade NHL with two courses of whole body irradiation of 0.75 Gy each followed 1 month later by involved-field irradiation (40 Gy in 20 fractions). Twenty-four patients achieved complete remission after LTBI and all patients except one were in CR after the localized involved-field irradiation. Nineteen patients remain alive and disease-free with a median follow up of 52.6 months. These results initiated a new EORTC clinical trial comparing involved field radiotherapy with LTBI+ involved field in early stage (I–II) low-grade NHL [43].

### 2.1. LTBI for pre-treated patients

LTBI was often used as a salvage therapy for pre-treated patients. The typical results were an overall response rate of around 60% and a complete remission (CR) rate of 25%. The 2- and 5-year actuarial survival reported were around 45 and 25%, respectively, with the best results achieved in those with low-grade histology [12,36,42,52]. These results were not very different from those achieved when LTBI was used ab initio. Indeed, a study of prognostic factors by Lybeert et al. has shown that neither survival nor RFS of unfavourable histological type was influenced by prior therapy. On the other hand, patients with favourable histology had a significantly better RFS if they received LTBI as primary therapy but survival was not significantly influenced [33].

### 2.2. Salvage therapy after LTBI

Mandehall et al. have treated 30 NHL patients relapsing after LTBI with either chemotherapy (25 patients) or a second course of LTBI (five patients). Both salvage treatments were equally effective. Twenty-three of the 30 patients obtained a second clinical response (complete and partial remissions). The median second disease-free survi-

val was 2 years. There were no treatment-related deaths and the most common complication was thrombocytopenia [36]. De Neve et al. reported that in patients relapsing after LTBI and receiving a variety of therapies the response rates were high, but of short duration, especially in intermediate or high-grade NHL. Also, the duration of response was progressively shorter after multiple relapses [9]. Johnson et al. reported that 17 relapsing patients who previously received LTBI have received subsequent chemotherapy (CVP). Despite that most of these patients also being given additional localized radiotherapy for their relapse, tolerance to CVP was excellent with most patients receiving full or only modestly attenuated doses [27]. Similarly, Dobbs et al. reported that chemotherapy subsequent to LTBI was given successfully to 31 of 37 patients. The remaining six patients were not able to tolerate chemotherapy because of prolonged thrombocytopenia. The authors had noted that all of these six patients had had an initial bone marrow involvement with the disease [12].

## 3. Comparing LTBI with chemotherapy

As the efficacy of LTBI became evident, Chaffey et al. compared the results of a LTBI-treated group with a historical group of chemotherapy-treated patients matched for age, sex and histology [6]. There was no difference in the 2-year actuarial survival between the two groups. Others started to randomise patients between LTBI and what was then considered the standard chemotherapy in the NHL and/or CLL such as CP, CHVmP, CVP, C-MOPP and CHOP. A list of these studies can be seen in Table 2.

In the EORTC lymphoma co-operative group trial, LTBI (1.5 Gy) + booster involved field radiotherapy was compared to combination chemotherapy (CHVmP) + consolidation irradiation to bulky sites. No significant difference in freedom from progression or survival was observed [35]. The British National Lymphoma Investigation (BNLI) compared LTBI with CHOP in stage III–IV, poor-histology (grade II) patients. Neither forms of therapy proved to be satisfactory and, although the group that received CHOP fared slightly better, the difference was not statistically significant [1].

Thus, in these and other reports, LTBI has been shown to be an effective treatment in controlling advanced stages of CLL and low-grade NHL for a prolonged period of time, with results comparable to the available chemotherapy to which it was compared [1,27,31].

## 4. Combining LTBI with chemotherapy

Very few studies have tried to combine LTBI and chemotherapy in the treatment of NHL. An early report on 34 patients randomized to either CVP + LTBI or CVP alone has shown that combining CVP with LTBI gave a 100% response rate, but the CR rate was similar to the CVP alone. With 14 months median follow-up no patients

in either arm of the trial have died, but relatively equal numbers have relapsed [56]. In 1979, two studies were published reporting the results of prospective pilot trials combining LTBI (1–1.5 Gy) with chemotherapy (CVP or C-MOPP) for previously untreated, stage II–IV, low-grade NHL patients [2,31]. Both trials reported minimal, acceptable toxicity and good results in terms of overall response (86–90%) and complete remission rates (60–80%). The number of patients, however, was very small (51 patients in both trials) and the results were not convincingly superior to those reported after chemotherapy alone.

Later in 1983, Weick et al. published the results of a single institution pilot study run by the Southwest Oncology Group (SWOG) between October 1977 and November 1978. In that study, a combination of CHOP and alternating LTBI was tried in 16 previously untreated patients with stage III and IV and diffuse-histology NHL. The total protocol consisted of four CHOP and three LTBI courses each of 0.45 Gy. This was a novel approach that had not been tried before. Responses were seen in eight of 11 (evaluable) patients, with six patients achieving CR. The median duration of these remissions was 15 months and the median survival of the entire group was 48 months. Given the standards of the late 1970s, these were encouraging results, comparable to those reported after more intensive CHOP alone [54]. The protocol was well tolerated and the toxicity was minimal. Despite these encouraging results, further studies along this line were not pursued. This study showed that LTBI given over a protracted period of time was still effective when given together with chemotherapy. It also proved that a TBI dose of 0.45 Gy did not compromise the bone marrow tolerance to the subsequent CHOP chemotherapy.

Combined LTBI and prednimustine were evaluated in two separate reports by the same authors in patients with either CLL or low-grade NHL (stage III–IV). Six to nine courses consolidation prednimustine were given 2 months after a LTBI dose of 1.5 Gy. The overall response rate was around 85% in both the CLL and NHL groups. The CR rates were 12 and 24% in the CLL and NHL patients, respectively [45,46]. The regimen was generally well tolerated and the authors concluded that it was an effective treatment for patients with CLL and advanced low-grade NHL. A list of these trials is seen in Table 3.

Combining LTBI with chemotherapy was also used with limited success in malignancies such as high-risk Ewing's sarcoma [30], and metastatic neuroblastoma [8], but with no success in advanced small cell lung cancer [11].

## 5. Side effects and complications of LTBI

In general, LTBI is devoid of any troubling acute effects such as lassitude, nausea and vomiting. The major acute effect to a cumulative dose of 1.5–2 Gy is thrombocytopenia and neutropenia. In an experimental study by Cowall et al.,

1.5 Gy of LTBI was given in 10 fractions over 5 weeks to six healthy beagle dogs and five dogs of various breeds with lymphoma. Bone marrow demonstrated significant reduction of granulocyte and macrophage progenitor cells during treatment with subsequent recovery towards normal pre-irradiation and sham irradiation values 4 weeks after treatment. When two additional dogs were injected with sub-lethal doses of *Salmonella typhosa* endotoxin, 2 weeks after completion of the irradiated regimen, their bone marrow GM-CFC responses were dramatically blunted compared to non-irradiated controls, whereas their peripheral leukocyte responses and serum CSF levels were comparable with non-irradiated controls. The authors suggested that LTBI-induced bone marrow injury might be clinically significant if patients are further stressed by infections or myelo-suppressive drugs [7]. In the clinical situation, the duration of such bone marrow injury seems to be around 2–3 months. In a study by Leimert et al. [31], when CVP was planned 45 days following LTBI (1.5 Gy), dose adjustment was needed for neutropenia and thrombocytopenia. Other studies have shown that, when subsequent chemotherapy was delayed by more than 2 months, it was not hampered by previous LTBI [12,33].

When 1.5 Gy LTBI is given to 26 previously untreated low-grade NHL patients with good performance status and early stage disease (stage I–II), the tolerance was excellent. The mean observed haematological nadir after completion of treatment was  $3.9 \times 10^9/l$  for granulocytes, 13.4 g/l for haemoglobin and  $124 \times 10^9/l$  for platelet count with a mean value of 3.2 months. All patients received the planned treatment without delay [43]. Giving the same dose of LTBI (1.5 Gy) to 12 NHL patients with advanced stage (III–IV) seemed to be less tolerated, since 3 patients needed dose reduction because of thrombocytopenia and leukopenia [31]. Another study from the Royal Marsden Hospital indicated that prolonged thrombocytopenia following LTBI appeared to be related to initially involved bone marrow [12]. There was also some evidence that the TBI-related toxicity is higher in the patients previously treated with chemotherapy or radiotherapy [41] and in high-grade lymphoma [9].

It is important to notice that in randomized trials, these LTBI-induced haematological complications were not very different from what was encountered following CVP and similar chemotherapy of the time [27].

Perhaps the most intensive LTBI protocol was that given by D'Angio et al. [8] to 14 children with advanced stage IV neuroblastoma. The TBI dose was relatively high and was given in close proximity to intensive chemotherapy (vincristine, DTIC, cyclophosphamide). Two patients died of toxicity and pronounced bone marrow depression, especially thrombocytopenia, which occurred after doses of 3–4.5 Gy. It is clear, however, that when using combined modalities it is very difficult to attribute toxicity to one specific part of the treatment schedule.

A major concern is that LTBI may increase the risk of

Table 2  
Studies comparing L-TBI with chemotherapy as first line treatment of NHL patients<sup>a</sup>

Reference (year)	Histological subtype	Stage	Treatment arms		Number of (evaluable) patients				Complete remission rate (%)				5-year survival (%)				5-year disease-free survival (%)			
			TBI (Gy)	CT	TBI	CT	TBI	CT	TBI	CT	TBI	CT	TBI	CT	TBI	CT	TBI	CT		
Chaffey et al. [6] (1975)	Nodular and diffuse <sup>c</sup>	III-IV 1.5	COP <sup>b</sup>		25	25	57	80	87 (3 years)	65 (3 years)	55 (3 years)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported			
Canellos et al. [3] (1975)	Nodular and diffuse <sup>c</sup>	III-IV 1.0-1.5	CVP		32	27	56	56	85 (3 years)	80 (3 years)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported			
Young et al. [56] (1977)	Nodular	III-IV 1.5	CVP		49	50	62	85	68	88	24	24	24	24	24	24	24			
Johnson et al. [27] (1978)	Diffuse PD <sup>c</sup>	III-IV 5.0-3.0	C-MOPP		22	29	69	69	52	42	13	13	13	13	13	13	13			
	Nodular		CVP		13	8	86	86	85	85	18	15	15	15	15	15	15			
	Diffuse <sup>c</sup>				17	17	77	77	28	25	5	0	0	0	0	0	0			
Hoppe et al. [18] (1981)	NPD/NM/DiffuseWD <sup>c</sup>	III-IV 1.5	CVP		48	66	71	88	92 (4 years)	88 (4 years)	35 (4 years)	30 (4 years)	30 (4 years)	30 (4 years)	30 (4 years)	30 (4 years)	30 (4 years)			
BNLJR [1] (1981)	Poor (grade II) <sup>c</sup>	III-IV 1.5	CHOP		6	15	23	39	18 (4 years)	30 (4 years)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported			
Jacobs and King [21] (1987)	WDL	III-IV 1.5	CP		6	15	67	67	80	25	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported			
	Follicular <sup>f</sup>				24	22	50	50	45	25	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported			
Meerwaldt et al. [35] (1991)	Follicular <sup>f</sup>	III-IV 1.5	CHVmP		44	40	36	36	45	65	15	25	25	25	25	25	25			

<sup>a</sup> All except the first study were prospective randomized trials. All the numerical differences between the two arms were not statistically significant. When the 5-year survival figure was not explicitly stated in the text of the original article the number was extracted from graphs.

<sup>b</sup> Comparison with a matched historical group.

<sup>c</sup> According to the Rappaport classification: PD, poorly differentiated; NPD, nodular poorly differentiated; NM, nodular mixed; WD, well differentiated.

<sup>d</sup> The British National Lymphoma Investigation Report.

<sup>e</sup> According to the Bennet, Henry and Farrer-Brown classification.

<sup>f</sup> According to the Working formulation: WDL, well-differentiated lymphocytic lymphoma.

Table 3  
Studies combining LTBI with chemotherapy in primary treatment of NHL<sup>a</sup>

Reference (year)	Histological subtype	Stage	No. of (evaluable) patients	LTBI dose (Gy)	Chemotherapy courses	CR rate	Median remission duration (months)
Leimert et al. [31] (1979)	Nodular	III–IV	11	1.5	Six CVP	55	9
Brereton et al. [2] (1979)	Nodular and diffuse	III–IV	20	1.0	CVP or C-MOPP	70	Not reported
Weick et al. [54] (1983)	Diffuse	III–IV	11	1.35	Four CHOP	55	15
Roncadin et al. [46] (1994)	Low grade	III–IV	41	1.5	Prednimustine (for 2 years)	25	16

<sup>a</sup> Chemotherapy was given after LTBI except in the study of Weick et al. where LTBI and chemotherapy were given alternatively. Toxicity was acceptable and no toxic deaths were reported.

secondary leukaemia after long observation periods [49–51]. However, late myelo-proliferative disorders seemed to occur after cumulative TBI doses in excess of 2 Gy [36] in the patients given extensive nodal irradiation as a supplement to TBI [23], or in patients receiving a combination of LTBI and alkylating agents [51].

## 6. LTBI: how does it work?

The idea of controlling a systemic disease with a total dose as low as 2 Gy is counterintuitive and hard to understand. Yet, it is possible, as described in the previous publications [4,5,12,16,33,36,37]. It is unfortunate that none of the previous clinical studies actually addressed the question of how LTBI works. Experimental data, however, suggest that the efficacy of LTBI could be explained by three mechanisms, namely, immune enhancement [13–15,32,38,44,48], induction of apoptosis [10,39,53], and the intrinsic hypersensitivity to low-radiation doses [34]. These mechanisms are not mutually exclusive and it is quite plausible that more than one mechanism can be functional at the same time.

### 6.1. Immunomodulation (radiation-induced immune enhancement)

In an investigation of the anti-tumour effects of LTBI in 1997, Hashimoto showed that 0.2 Gy of TBI suppressed growth of implanted tumours during the first 7 days after TBI. Metastasis to the lungs and lymph nodes were also significantly reduced by LTBI. When the lungs were shielded using 5-cm lead blocks, the suppression of lung metastasis by LTBI was the same as that in the non-shielded group. These results suggested that LTBI brought about anti-tumour effects through host immune response, unlike those produced by high-dose irradiation [14]. Further evidence on the suppression of metastasis and the change in the immune response after LTBI is found in the most recent paper by Hashimoto et al. [15] as well as in other publications [19,47]. Experimental animal data proved that LTBI could

- augment the proliferative reactive response of T cells to

antigenic, allogenic and mitogenic stimulation as well as increase the cytotoxic activity to tumour cells [20,32];

- alter cytokine release, particularly the activation of interferon- $\gamma$ , and IL-2 production [13,15,48].

In an important clinical study by Yonkosky et al., nine NHL patients who had failed previous chemotherapy were treated with fractionated LTBI (1.2–1.8 Gy). Prior to, during and after scheduled therapy, peripheral blood samples were taken to measure the proliferative responses to mitogens. The study showed that LTBI seem to enhance, rather than suppress, the in vitro immune response in several patients. The mitogen responses were 127–319% over initial values for all five patients with complete response. By contrast, mitogen responses were not improved in the patients with unchanged or progressive disease, thus demonstrating that LTBI could induce a certain degree of immune enhancement in humans [55].

A recent review on the immune biology of LTBI is being prepared for publication elsewhere (A. Safwat, Radiation Research, accepted 2000).

### 6.2. Induction of apoptosis

Lymphocytes are known to undergo apoptosis in response to radiation exposure. In 1992, Nomura et al. detected programmed cell death in the thymus and spleen of various mouse strains following LTBI in the range of 0.05–0.5 Gy [39]. In a study on patients treated by therapeutic TBI, Delic et al. have shown that the commitment to apoptosis can be determined after 2 Gy. They also showed that the susceptibility to apoptosis induced by ionising radiation may be related to the type of haematological malignancy and/or previous administration of chemotherapy [10].

### 6.3. Hypersensitivity to low-radiation doses

The phenomenon of low-dose hypersensitivity (HRS) and induced radio-resistance (IRR) was demonstrated in the low-dose survival work of many normal hamster and human cells and a large number of human tumour cell lines from a number of laboratories. It describes low-dose

hypersensitivity detected after single doses of X-rays less than 0.3 Gy and the subsequent increased radio-resistant response seen as the dose was increased up to 1 Gy. The working hypothesis for the biological mechanisms controlling this phenomenon is that increased radio-resistance is a consequence of an inducible radio-protective mechanism triggered by an increasing level of damage. Therefore, cells are hypersensitive to X-ray doses that produce insufficient damage to activate this process [34]. If this phenomenon is functional in lymphomas, then one may assume that the repetition of the small doses given in low-dose TBI would capitalise on the hyper-sensitivity phenomenon and would increase the cell kill, leading to its well-documented clinical effects.

## 7. Future prospects

LTBI is a conceptually challenging form of treatment. Seen in the light of the conventional chemotherapy and conventional 'high-dose' radiotherapy, LTBI seems to provide an 'alternative' mechanism(s) of action against cancer cells. Hence, the logical assumption that given in conjunction with a standard treatment, the results would be additive or hopefully synergistic. Despite its undoubted efficacy, LTBI is an under-investigated and under-utilized treatment modality. The optimal exploitation of this modality in treatment of NHL and other malignancies is hampered by the lack of a comprehensive view of its mechanisms of action and its possible synergism with chemotherapy, biological response modifiers and/or immunotherapy.

What make LTBI particularly attractive are the following advantages:

1. It is a cheap and non-toxic treatment. Its major acute problems, which are thrombocytopenia and neutropenia, are dependant on predictable factors such as patient's performance status, the total dose, treatment intensity (duration of LTBI schedule), previous chemo- and radiotherapy, and bone marrow involvement by the disease. It is usually mild to moderate and reversible.
2. The dose used is well below the tolerance of all organs and should not alter any proposed salvage therapy even if it includes TBI and BMT.

The lack of any substantial breakthrough in the outcome of treatment of NHL in the last decade should encourage researchers to integrate LTBI in new and innovative experimental treatment protocols of NHL. The reported increased incidence of secondary leukaemia that may occur when LTBI is combined with alkylating agents and/or total lymphoid irradiation should be kept in mind when designing such protocols. This complication could exert some limitations on the use of LTBI in highly curable disease and young patients in whom long-term survival is expected.

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