Time to rejuvenate ultra-low dose whole-body radiotherapy of cancer

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A R T I C L E   I N F O

A B S T R A C T

The results of clinical trials performed from the 1930s until the end of the 20th century in which total-body ultra-low level ionizing radiation (TB-LLR) was used demonstrate that this form of treatment can be equal or superior to other systemic anti-neoplastic modalities in terms of the rates of remissions, toxicity, and side effects. In this review, we provide the rationale for TB-LLR and analyze the results of reliable clinical trials in patients with predominantly lymphoproliferative disorders but also advanced solid cancers. The doses used in these trials did not exceed 0.1–0.2 Gy per fraction and cumulative totals ranged from 1 to 4 Gy. Based on the reviewed results we conclude that it is appropriate to revive interest in and resume clinical investigations of TB-LLR in order to refine and improve the effectiveness of such treatment, whether employed alone or in combination with other anticancer strategies.

1. Background and rationale

One of the major methods of cancer treatment is radiation therapy (radiotherapy, RT) which employs ionizing radiation delivered at doses that kill malignant cells. Currently, RT is used routinely as a standard treatment for more than 50 % of cancer patients (Delaney et al., 2005; Jaffray, 2012; Yaromina et al., 2012). Conventional high-dose radiation therapy can be curative in a number of radiosensitive neoplasms if they are localized to one major area of the body. The typical total dose (in standard 1.8 Gy–2 Gy fractions) for a solid epithelial tumor (a carcinoma) ranges from 60 to 80 Gy, while bulky lymphoma sites are irradiated at doses from 20 to 40 Gy (again in 1.8 Gy–2 Gy fractions) (Kimball and Webb, 2013). The total dose is fractionated to afford normal cells time to recover, while tumour cells are generally less efficient in repair between fractions. Fractionation also allows malignant cells that were in a relatively radio-resistant phase of the cell cycle during one treatment to move into a sensitive phase of the cycle before the next fraction is given. Similarly, tumour cells that were chronically or acutely hypoxic (and therefore more radioresistant) may reoxygenate between fractions, improving the tumour cell kill (Ang, 1998).

Over recent years much attention has been focused on yet another aspect of radiotherapy, i.e. its effects on the immune system, a crucial player in any organism's control over the development of neoplasms (Corthay, 2014). After years of controversies, the early concept of cancer immunological surveillance, whereby specifically stimulated (adaptive) immunity wards off proliferation of neoplastically transformed cells, has now been incorporated into the modern concept of cancer immunoediting. During the three phases of this process, both the tumour-associated immune system (TAIS) and immunogenic properties of cancer cells are being gradually 'edited.' As a result, various elements of TAIS which *protect* the host against the development of a malignancy during the initial 'elimination' phase (and later, during the following 'equilibrium' and particularly 'escape' phases), morph into active *supporters* of cancer progression and the tumour cells become more and more resistant to assaults from the TAIS. Consequently, the growing tumour not only evades immune recognition and destruction, but also actively contributes to remodeling of its microenvironment towards the immunosuppressive and pro-neoplastic state (Dunn et al., 2002, 2004; Schreiber et al., 2011). This improved understanding of the relationship between a developing neoplasm and the immune system has shed new light on the recently acknowledged complex interactions of ionizing radiation with cancer-related immunity. This, in turn, has led to the development of novel radiotherapeutic schemes based on the notion that local exposures at moderate (between 0.2 and 2.0 Gy absorbed during a short time, i.e., acute, exposures) or even higher (over 2.0 Gy) doses of radiation can, especially in combination with standard immunotherapy, stimulate various anti-neoplastic immune reactions, and/or reverse the suppressed state of TAIS. These effects are thought to result from the

radiation-induced 'immunogenic' cell death, inflammation, and tissue injury, all leading to the emergence of 'danger signals' which prompt anti-cancer functions of various elements of the immune system (Janiak et al., 2017; Griffin et al., 2020). It is currently believed that RT-activated immunity is responsible for regression of non-irradiated metastatic lesions outside of the irradiated field (the abscopal effect) (Yilmaz et al., 2019).

However, radiotherapy at moderate to high doses is potentially harmful to normal cells and tissues and may lead to immunosuppression and/or the development of secondary cancers (Tubiana, 2009; Gudowska et al., 2014; Casey et al., 2015; Ng and Shuryak, 2015). Nevertheless, such untoward effects are highly unlikely after exposures at low doses or dose rates (i.e., at ≤0.1 Gy absorbed acutely or at rates of ≤0.1 mGy/min applied during a protracted exposure) of low linear energy transfer (LET) ionizing radiation (X- or γ-rays), hereafter referred to as low-level radiation (LLR). It has been demonstrated that the effects of LLR, including modulation of the immune functions, qualitatively and quantitatively differ from those induced by moderate-to-high doses of X- or γ-rays (Albrecht et al., 2011; Yu et al., 2013; Wodarz et al., 2014; Yang et al., 2016). Notably, single or multiple exposures to LLR (delivered over many weeks and totaling 1−4 Gy) can be safely applied to hemi-body or whole-body, making it a good treatment of choice for patients with systemic neoplasms such as lymphomas and leukaemias or solid tumours with multiple metastases. Indeed, as evidenced by results of many epidemiological and experimental studies, including our own, total-body exposures to LLR (TB-LLR) can inhibit or retard the development of both primary and metastatic cancers in various oncological settings (Janiak et al., 2017; Yang et al., 2016). The possible mechanisms by which such protective effects are mediated involve LLR-induced scavenging of reactive oxygen intermediates, stimulation of the repair of the DNA damage (including that caused by normal metabolism and proliferation of a cell), mitigation of inflammation, triggering of selective apoptosis and/or senescence of aberrant cells and, last but not least, triggering and amplifying the function of the immune system (Bauer, 2007; Scott, 2008, 2014; Feinendegen et al., 2012; Cui et al., 2017). In fact, it has been repeatedly demonstrated that whole-body exposures of mice and rats to LLR stimulate both the innate and adaptive arms of anti-cancer immunity including the activity of various subsets of T, B and NK lymphocytes, macrophages, dendritic cells, neutrophils, mast cells, and other elements of the immune system (Janiak et al., 2017; Yang et al., 2016; Cui et al., 2017). Arguably, stimulation of anti-neoplastic immunity has been responsible for the effectiveness of whole- and half-body irradiations at low doses of X- or gamma-rays of oncological patients performed for over one hundred years (see the data below and in Table 1).

2. Methods

For the purpose of this review we conducted a PubMed search as a starting point but we also searched other databases such as Cochrane Library, Medline, and Google Scholar. In all the search queries we covered the period from the beginning of the 20th century until 2020. As a search strategy, a combination of terms such as low level or low dose total/whole-body radiation with cancer/malignancy treatment and radiotherapy was employed. The selected articles were classified according to the presupposed criteria of the ultra-low doses, i.e., those which for the short-term exposures did not markedly exceed 0.1 Gy per fraction delivered to either a whole or half of the patient's body. This way, many papers with titles or abstracts alluding to "low" doses which did not meet these criteria were disregarded. In the great majority of the cases only references for which full texts could be obtained were reviewed.

As experts in the field, we are aware of several references that are not routinely carried in the popular search engines. Many of the older papers have been overlooked so we have resurrected them from other papers and included them in this review. We did not restrict ourselves

exclusively to prospective randomized clinical trials but we also included reliable single-institution series, retrospective reviews, phase I/II studies, and case reports to make this review as comprehensive as possible. The results of the search have been presented in Table 1, which is composed of the most important and relevant findings including patients' characteristics, treatment schemes and results and side effects thereof, with special emphasis on the comparison of these with the effects of systemic chemotherapy and/or local high-dose radiotherapy. The extended description of the results of the critical trials has been included in chronological order in the main text of the review.

3. The past and present of clinical trials

The concept of total-body irradiations (TBI) with X-rays is an old idea. In fact, in view of the early recognized widespread nature of many human malignancies the idea was hit upon soon after the Roentgen's discovery and already in 1905 first arrangement of three low voltage X-ray tubes distributed around a room to achieve uniform irradiation of a centrally placed patient was designed in Germany. This set-up was soon used by Friedrich Dessauer to treat human patients (Dessauer, 1905). The results of that first reported clinical trial were encouraging, but the initial enthusiasm was abated by the discovery of suppressive effects on the haematopoietic system. A little later, in the early 1920s, Chaoul and Lange reported in Berlin on the effects of *teleroengenotherapy* of patients with advanced Hodgkin's disease. All twelve patients so treated showed 'restoration to their full working capacity' and ten of them remained free from recurrence for 2.5 years on average (Chaoul and Lange, 1923). In the second half of the 1920s, Werner Teschendorf treated patients with leukemias, lymphomas, and polycythemias using one X-ray tube to deliver 200–250 R (roughly equivalent to 2−2.5 Gy) to the patients' whole bodies. The author noted 'greater remission periods in these diseases then by using small ports in the ordinary way' (Teschendorf, 1927). On the turn of 1920s and 1930s Schwartz obtained 'excellent results' in patients with slowly developing Hodgkin's disease after eight to ten exposures to 'small protracted roentgen-ray dosage' given within 14 days (Schwartz, 1930). Also, Frimann-Dahl and Forsberg, who exposed the entire bodies of patients with leukemias to 'interrupted dosage' of X-rays at about 0.75–6 Gy delivered daily over the period from four days to five weeks, concluded that 'general irradiation (meaning TBI) is superior to local roentgenotherapy because it is more lenient, enabling the patient to keep up his work longer' (Frimann-Dahl and Forsberg, 1931). The encouraging results of these trials prompted physicians in other European countries, such as Norway, France, Austria, Belgium, and Italy, to use subtotal- and total-body X-ray irradiations of patients with various haematological malignancies (Dale, 1931; Devois, 1931; Sluys, 1931; Pulsford, 1932; Palmieri, 1933; Mallet, 1936; Sgalitzer, 1936; Jacob, 1939; Marqués and Betouliéres, 1949).

In the USA, the first systematic clinical trials with total-body exposures to ionizing radiation were conducted in the early 1930s by Arthur C. Heublein. For these trials patients at the Memorial Hospital of New York were placed in beds in a specially built 'lead-lined radiation ward' and irradiated either continuously or intermittently from a Coolidge therapy tube. Altogether, 13 patients with lymphomas or leukemias and 17 patients with disseminated solid cancers were exposed to X-rays at dose-rates of approximately 0.01 Gy/h (continuous irradiation) and 0.3 Gy/h (intermittent irradiation) up to the total absorbed doses of about 0.4–1.9 Gy and 7.5−10 Gy, respectively (Heublein, 1932). As reported by the author 'definite regressions have been noted in the radiosensitive group of cases' including both haematological and solid cancer patients who showed 'no depression in the number of white cells' after 'administration of amounts of radiation ranging from 5 to 25 per cent of an erythema dose (i.e., about 7.5 Gy) to the entire body.' In summary, Heublein wrote that although the number of cases in both groups of the patients was too small to permit any definite conclusions 'the evidence accumulated thus far fully warrants the continuation of the experiment with increasing dosage, within safe limits.' Unfortunately, these trials

Table 1

Reported reliable clinical trials with total- or hemi-body irradiations with X- or gamma-rays in patients with various malignancies.

Patients/diseases	Treatment	Results	Side effects	Ref.
13 patients with lymphomas or leukemias and 17 patients with disseminated solid cancers	a) *long distance continuous irradiation* with X-rays at dose rate of approx. 0.01 Gy/h up to total of 0.38−1.9 Gy delivered over 7.5−13.9 days (20 patients); b) *short distance intermittent irradiation* with X-rays at dose rate of approx. 0.3 Gy/h up to total of 7.5−10 Gy delivered over 12−24 days (10 patients)	a) "distinct improvement" in 2 breast ca cases (out of 8 solid cancer patients), in 1 lymphatic leukemia and 1 HD patient; "partial improvement" in 1 case of lymphatic leukemia b) CR in 3 out of 9 patients with solid cancer.	"repeated blood counts and other tests have, in all instances, failed to show any consistent change that could be ascribed to radiation effect, except in the leukemias, in which the usual decrease in the number of white cells has occurred. There has been no instance of marked drop in blood platelets nor has purpura hemorrhagica occurred in any case; with the administration of amounts of radiation ranging from 5 to 25 per cent of an erythema dose to the entire body, there has been no depression in the number of white cells."	(Heublein, 1932)
270 patients with a variety of tumours (lymphomas, leukemias, multiple myelomas, carcinomas, sarcomas)	TBI with X-rays at 0.5−0.75 Gy ("Heublein technique") usu. after local X-ray therapy	patients with lymphomas exposed earlier to local X-ray therapy had both longer survival and longer-lasting remissions than patients who received only local X-ray irradiation.	NR	(Medinger and Craver, 1942)
163 patients with granulocytic and lymphocytic CL	TBI with X-rays at 0.1−0.2 Gy/ exposure given in 6−17 individual exposures to total doses of 0.9−3.5 Gy (23 patients) or equivalent internal TBI by iv injection of P^{32} (140 patients)	survival of the low-level radiation-treated patients "significantly better than that for a collected series including all radiation treated cases reported in the literature from 1925 to 1951"; no significant difference between the effects of X-rays and P^{32}	"no radiation sickness"	(Osgood et al., 1955)
52 patients: 7 with CL, 8 with AL, 15 with lymphoma, 16 with advanced solid tissue cancer, 6 with polycythemia vera	single or fractionated TBI with X-rays at 0.05 to 1 Gy (CL and lymphoma patients), 3 Gy (AL patients), 3−8 Gy solid cancer patients)	among the 7 CL patients: excellent response (in terms of survival) in 1 patient, good response in 2 patients and questionable response in 1 patient	nausea and/or vomiting in 18 patients, transient TCP and lymphocytopenia, otherwise no serious side effects	(Jacobs and Marasso, 1965)
19 patients: 7 with CLL, 5 with generalized lymphoma, 3 with mycosis fungoides, 2 with AL, 1 with mixed lymphoma, 1 with macroglobulinaemia	TBI with X-rays at 0.05−0.2 Gy/ daily for several days to total of 1−4 Gy or 0.1−0.2 Gy given bimonthly	"satisfactory improvement" (a minimum decrease of 75 % in clinically measurable disease + symptomatic improvement) in 5 CLL patients, 4 lymphoma patients (in 3 without prior CT or RT) and 1 AL patient	except for transient TCP and lymphocytopenia no significant symptoms or side effects	(Johnson, 1966)
27 patients with stage III and IV (marrow) previously untreated NHL	18 patients treated with either TBI alone (γ-rays at 0.1 Gy daily 3−5 times/ wk to total of 1−3 Gy) or with TBI followed 3 mos. later by TNI (at a total of 20−35 Gy applied in daily fractions of 1.5−2 Gy)	CR in 25 (93 %) patients; median duration of unmaintained remission = 26 months	transient bone marrow depression requiring blood transfusion in 4 of the 18 patients treated with either TBI alone or with TBI + TNL	(Johnson, 1972)
61 patients (37 males and 24 females) with CLL	a "life-time" series of X-ray irradiations consisting of: 1) 10 daily TBI at 0.1 Gy, 2) 1 weekly TBI at 0.05 Gy, 3) an annual "booster" of 10 daily TBI at 0.1 Gy, and 4) regional irradiation of spleen or lymph nodes as required. Patients kept on this regimen for 3−7 y (total doses of 11−28 Gy)	average survival 46 mo, with a maximum of 15 y, a 5-y survival of 21% of patients	transient leukopaenia and TCP; autopsies performed in 1/3 of the patients revealed "no instance of untoward radiation effects in BM or other structures examined."	(Del Regato, 1974)
65 (59 evaluable) patients with lymphocytic lymphoma (20 stage III and 45 stage IV) randomized to treatment with CT or RT: 27 evaluable combined (CVP) CT patients and 32 evaluable RT patients	RT group: only TBI (0.1 Gy of γ-rays daily for 3−5 days/wk to total of 1−5 Gy) in 21 patients; only TNI (20−30 Gy within 2−4 weeks) in 6 patients; TNI preceded by TBI (at a total dose of 1.5 Gy) in 2 patients; either HBI or TNI + localized irradiation in 4 patients; CT group: 32 patients given cytoxan (400 mg/m^2 x 5 p.o.) + vincristine (1.4 mg/m^2 i.v. on day 1) + prednisone (100 mg/m^2 x 5 p.o.) − 6 times every 21 d.	RT group: CR in 18 (56 %) patients (9 relapsed with a median duration of remission = 22−31 mos), PR in 8 (25%) patients, NE in 6 (19%) patients – no data on CR and PR in patients treated solely with TBI; CT group: CR in 15 (55%) patients (7 relapsed with a median duration of remission >12 mos), PR in 9 (33%) patients, NE in 3 (11%) patients	toxicity of TBI as described above by Johnson 1972; toxicity of the CVP regimen: granulocytopaenia following each cycle and TCP < 100,000 mm^3 (rare in the first 6 cycles); neurotoxicity of some degree	(Canellos et al., 1975)
39 patients with well (6) and poorly differentiated (23) lymphocytic lymphoma	31 patients treated only with TBI (0.1 Gy of X- or γ-rays/ fraction to a total of 1.0−1.5 Gy), 8 patients treated with TBI followed by TNI (10 Gy to involved lymphatic areas)	CR in 68 % of TBI-only patients and 75 % of TBI + TNI patients	"moderate-degree and transient hematological depression" induced by TBI	(Johnson, 1975)
				(Kazem, 1975)

Table 1 (*continued*)

Patients/diseases	Treatment	Results	Side effects	Ref.
4 patients with stage III NHL 2 with refractory CLL, 2 with disseminated mycosis fungoides, 1 with post-CT relapsed end-stage reticulum cell sarcoma	TBI at doses 0.15 Gy of γ-rays daily for 5 d, then at 0.1−0.15 Gy every other d, or at longer intervals over 5−12 wk to total doses of 2.0−2.65 Gy	80 %, 90 %, and 95 % "nodal regression" in 3 patients with previously untreated stage III NHL; PR in 4th patient previously treated with CT, but the treatment stopped at 1.05 Gy due to persistent TCP; "dramatic regression" of active lesions all over the body of 1 patient with mycosis fungoides	"no obvious subjective or objective complications" except for "moderate and reversible BM depression"	
51 patients with stage III and IV lymphocytic lymphoma who received TBI as the initial and only therapy	TBI with X-rays at 0.15 Gy twice weekly to 1.5 Gy total dose + IFRT in patients with persistent local tumours; initial 25 TBI-treated patients were compared to a matched group of patients treated with CVP	CR up to 80 % of the TBI-treated patients; with a median survival >32 mos and 83% and 68% actuarial survival at 3 y and 5-y, respectively; no statistical difference between the TBI and CT groups in terms of survival, but "the trend favored irradiation"	transient thrombocytopenia and leukocytopenia; no nausea, weakness, hair loss, or malaise	(Chaffey et al., 1976; Chaffey et al., 1977)
57 patients with progressive CLL: 42 patients treated only with TBI, 14 evaluable patients treated with TBI + CT	TBI alone (42 patients): series of irradiations with 0.5 Gy of γ-rays given in fractions (0.05−0.1 Gy daily, 3−5 times/week) separated by 4−8-wk intervals up to total doses of 1−4 Gy; TBI + CT (14 evaluable patients): 12 courses of CP and prednisone daily	TBI alone patients: CR in 14 (33 %) patients, PR in 23 (55 %) patients; median survival: 72 mo (patients with stage I-II disease) and 63 mo (patients with stage III-IV disease); TBI + CT patients: CR in 8 (57 %) patients, PR in 5 (36%) patients; median survival: not determined yet	TBI alone patients: modest anemia in 5% and modest thrombocytopenia in 15 % of the patients, no hemorrhagic problems; TBI + CT patients: "treatment tolerated extremely well, no hematologic toxicity requiring transfusion support"	(Johnson, 1976, 1979)
48 patients with previously untreated stage III and IV lymphocytic, lymphoblastic, and mixed histology NHLs (15 with diffuse and 33 with nodular disease)	TBI with X-rays at 0.15 Gy twice a week until 1.5 Gy or a haematologic depression; 25 patients were compared to a matched group of patients treated with CVP	> 70 % actuarial survival of the first 25 patients treated with TBI alone vs. approx. 31 % survival of the matched 25 patients treated with combined CT (CVP)	in TBI patients: no nausea, vomiting, hair loss, or bleeding; toxicity limited to transient TCP	(Hellman et al., 1977)
9 NHL patients: 7 with LL and 2 with HL who had previously failed on CT	TBI twice a week at 0.15 Gy of X-rays to a total dose of 1.2−1.8 Gy	CR in 5 patients (71 %) with LL, PD in 1 patient with LL and in 2 patients with HL; NE in 1 patient with LL; clinical response correlated with restoration of mitogen proliferative responsiveness of circulating blood lymphocytes	NR	(Yonkosky et al., 1978)
58 previously untreated patients with stage III or IV NHL (43 patients with nodular and 15 with diffuse histology)	TBI at 0.15 Gy of X-rays twice a week to a total of 1.5 Gy; (24 patients with persistent localized masses received additional local irradiation at 1.0−2.0 Gy)	30 patients (52 %) survived 8 y (57 % with nodular and 42 % with diffuse histology); 8-y relapse-free survival in 8 (14 %) patients (median time to relapse – 21 mos)	thrombocytopenia (in all but 4 patients rebounded to near normal values within 1 mo); 2 cases of erythroleukemia (EL), both treated with a 2nd course of TBI and combined CT before the development of EL	(Carabell et al., 1979)
39 patients with advanced NHL: 38 with nodular (30) or diffuse (8) LL and 1 with nodular ML (28 patients with no previous treatment, 11 patients in relapse after CT or local RT)	TBI at 0.10 or 0.15 Gy of γ-rays twice a week to a total of 1.5 Gy	CR in 33 (85 %) patients with median duration 24 mos, PR in 6 (15%) patients	significant thrombocytopenia (platelet count < 50,000 /mm³) in 12 (31%) patients and significant leukopenia (WBC < 1,500/mm³) in 3 (8%) patients; "no cases of myelogenous leukemia to date"	(Choi et al., 1979)
30 patients with stage III (6 cases) and IV NHL (24 cases); 11 patients had previous local RT (4), CT (6) or both (1)	TBI with X-rays at 0.1 Gy 3 times a week until the total dose of 3.0 Gy;	CR in 10 of 19 (53 %)* of patients who had no previous treatment, but in 10 of 13 (77 %) non-leukaemic patients with no previous treatment *compared to ca. 40% treated with polyCT (de Vita et al. Lancet 1975)*	no vomiting or diarrhea, toxicity confined to haematological depression (generally acceptable in non-leukaemic patients, but severe in some leukaemic patients) *TBI very well tolerated compared to CT; TBI may be applied if CT does not give full remission*	(van Dijk-Milatz, 1979)
33 patients with NHL: 30 with lymphocytic lymphoma (24 with poorly differentiated diffuse type and 6 with well-differentiated nodular type) and 3 with histiocytic lymphoma	TBI at 0.1 Gy of X-rays 3 times per week to total dose 1.8−2.2 Gy; 14 patients additionally treated with IFRT at 10−15 Gy	CR in 25 (83 %) patients and PR in 5 (17 %) patients with lymphocytic lymphoma; 2 PR in 2 patients and NE in 1 patient with histiocytic lymphoma	transient pancytopenia with thrombocytopenia – recovery in all but 2 cases; no other toxicity or malaise associated with TBI	(Qasim, 1979)
48 previously untreated patients with stage II-IV NHL (63 % with nodular and 36 % with diffuse histology) and 15 patients previously treated with localized RT (6 patients) or CT (9 patients)	TBI at 0.1−0.15 Gy/d of γ-rays 2−5 times per week to a total of 1−1.5 Gy; then after a 4−6-week split another course of TBI (16 patients with persistent localized masses received additional local irradiation at 1.0−2.0 Gy)	CR in 80−85% of patients with nodular lymphoma and in 33−43% of patients with diffuse lymphoma; PR in 10−20% of patients with nodular and in 50-100% of patients with diffuse lymphoma; NE in 2 (4%) of all 48 patients (the 4-y actuarial survival was 71% for the nodular group and 57% for the diffuse group); patients previously treated with	TCP (<30,000 platelets/mm³) in patients with both a positive BM and an enlarged spleen; no acute systemic side effects (i.e., nausea, vomiting, diarrhea, hair loss); no secondary leukemia seen	(Thar et al., 1979)

Table 1 (*continued*)

Patients/diseases	Treatment	Results	Side effects	Ref.
26 patients with stage III (6 cases) or stage IV (20 cases) NHL previously treated with CT and/or local RT	20 patients: TBI with γ-rays at a total dose of 1.5 Gy given in 15 fractions, 5 patients: TBI at a total dose of 1.25 Gy given in 11 fractions; 1 patient TBI at a total dose of 1.2 Gy given in 14 fractions + HBI at 0.6 Gy	RT or CT: CR in 60%, PR in 13%, NE in 26% of the patients (actuarial survival = 55% at 2 y) CR in 6 (23 %) and PR in 11 (42 %) of the patients; actuarial survival = 55 % at 1 y and 42 % at 30 mos	TCP and less pronounced leukopaenia 3–6 wks after completion of TBI ("apparently influenced by previous cytotoxic therapy") with return to normal 3–4 wks later; apart from some minimal hair loss no other side effects, including no GIT; "no serious sequeale"	(Rees et al., 1980)
37 patients with advanced NHL (22 with nodular and 15 with diffuse type): 31 with lymphocytic lymphoma, 4 with mixed lymphocytic-histiocytic lymphoma and 2 with undifferentiated lymphoma; 24 patients without previous therapy and 13 in relapse after previous CT or local RT	TBI at 1.5 Gy of X-rays in mid-plane dose given in 10 fractions over 12 d (13 patients); PTBI at 1.5 Gy mid-plane dose in 10 fractions twice wkly for 5 wk (13 patients); HBI* at 3 Gy in 10 fractions for 12 d, other half 6–8 wks later (11 patients)	in patients with nodular disease: CR in 14 (64 %) and PR in 2 (9%) patients; in patients with diffuse disease: CR in 6 (40 %) and PR in 6 (40 %) patients, NE in 9 of all the patients; overall response rates: 80 % (12 of 15) for the diffuse and 73% (16 of 22); HBI more effective (64% CR and 16 mos median duration of response) compared to TBI (54% CR and 10 mos median duration of response) and PTBI (38% CR and 14 mos median duration of response)	TCP (<50,000 platelets/mm³) in 14 (38%) patients, no serious bleedings	(Dobbs et al., 1981)
51 patients with "favourable histology" stage III-IV NHL	17 patients: TBI with X-rays (2–3 times/wk with a weekly dose of 0.3 Gy to a total of 1.5 Gy followed by a "boost" of 20–30 Gy in 2–3 wk to each site of pathologic involvement excluding BM); 17 patients: single alkylating (SA) agent (CY or chlorambucil) daily until CR; 17 patients: several cycles of CVP every 21–28 days until CR	TBI patients: initial CR (iCR) in 12 (70.1 %) patients, continuous CR (cCR) in 6 (35 %) patients; SA patients: iCR in 11 (65 %) and cCR in 6 (35 %) patients; CVP patients: iCR in 15 (88%) and cCR in 8 (47%) patients;	in TBI with a "boost" patients: persistent cytopaenia (either WBC count <3000/mm³ or platelet count <100,000/mm³ for ≥ 6 mo) in 5 (29%) patients, transient TCP (platelet count <50,000 mm³) and leukopaenia (WBC count <2000 mm³) in 3 (17.6%) patients; no other serious maladies/toxicities	(Hoppe et al., 1981)
91 patients with generalized NHL, HD, CLL, CML, myelomas, seminomas or SCLC (most of the NHL patients, all patients with HD and CLL and 2 of myeloma patients previously failed to respond to or recurred after previous CT and/or local RT)	29 patients given TBI (0.1 Gy daily to a total doses of 1–5 Gy without shielding of the skull and extremities); 62 patients given fractionated STBI (0.5 Gy daily for 5 d/wk up to the total of 1–40 Gy given as a single or repeated treatment)	long-term ("occasionally up to 17-y or permanent") remissions in patients with NHL, HD, leukemias, myelomas and seminomas treated with TBI or STBI	transient depression of peripheral blood counts in patients receiving 1–1.5 Gy at 0.1–0.15 Gy/d; otherwise "little or no treatment-induced symptomatology"	(Loeffler, 1981)
14 children with metastatic (stage IV) neuroblastoma	TBI with X-rays at 1.0–1.5 Gy/cycle in 0.5 Gy daily fractions delivered in 2–3 cycles along with 3-wk cycles of standard CT (vincristine, DTIC, cyclophosphamide)	4 of 12 (29 %) patients free of disease for 12+ to 31+ mo; 2 patients died of BM toxicity	pronounced TCP requiring platelet transfusions after the 2nd and subsequent cycles of treatment; otherwise "most patients remained in good health"	(D'Angio and Evans, 1983)
24 patients with high-risk Ewing's sarcoma (clinically radioresponsive)	after 2–3 cycles of combined CT and 5 cycles of local RT patients were exposed to TBI at 0.15 Gy fractions of X-rays twice a week for 5 weeks to a total dose of 1.5 Gy followed by intensive CT and autologous BM transplant	CR in 20 (83 %) patients (approx. 70 % of the patients relapsed and died)	"TBI was well tolerated. An occasional patient required an oral antiemetic to control nausea, but no significant vomiting, abdominal cramping or diarrhea occurred."	(Kinsella et al., 1983)
108 patients newly diagnosed with indolent lymphoproliferative diseases: CLL (41 cases), stage III and IV well-differentiated LL (21 cases), and stage III and IV FL (46 cases)	54 patients exposed to TBI with γ-rays (0.15 Gy 2x/wk to total of 1.5 Gy) and 54 patients treated with CT (chlorambucil 0.15–0.2 mg/kg orally/d to hematologic tolerance + prednisone 0.5 mg/kg orally/d for the 1st mo)	CR of 59 % and 52 % and median survival of 53 and 57 mo in CT and TBI patients, respectively; the equivalent outcomes remained after stratification into CLL, LL, and FL	negligible morbidity (myelotoxicity); no cases of acute leukemia in both groups of patients	(Jacobs and King, 1987)
68 NHL patients (34 with low, 10 with intermediate, and 19 with high grade malignancy); TBI the first treatment for 47 patients, 21 patients failed on CT or/and standard RT before being accepted for TBI	TBI at 0.1 Gy of X-rays/fraction 3 times/wk., to total doses of 1.8–2.2 Gy	84 %, 42 %, and 40 % CR rates for low, intermedia-te, and high-grade NHL, respectively; better remission rates in patients exposed to TBI as the initial treatment than in the earlier pretreated patients	transient TCP and leukopenia; no other side effects such as nausea, vomiting, or hair loss	(Lybeert et al., 1987)
60 patients with stage II-IV NHL (excluding diffuse histiocytic lymphoma: 44 patients treated de novo (DN) and 16 treated previously and relapsed (PT)	TBI at 0.10 Gy of γ-rays/d, five days/wk, for 2–3 wks followed by a treatment split and another 1–2 Gy delivered in the same manner (regimen A, 35 patients) or 0.15 Gy 2x/wk to a total of 1.5 Gy without a treatment split (regimen B, 9 patients); 16 patients additionally	DN patients: CR in 20 of 26 (77 %) and in 6 of 17 (35 %) patients with favourable (FH) and unfavourable (UH) histology, respectively; PR in 6 of 27 (22 %) and in 11 of 17 (65 %) patients with FH and UH, respec-tively; NE in only 1 patient; survival rates at 2-, 5-, and 10-y for	TCP (< 50,000 platelets/mm³) in 15 (34%) DN patients; 4 "probable cases" of MPD (developed 2.7–6 y after TBI); no secondary leukemia cases!	(Mendenhall et al., 1989)

Table 1 (*continued*)

Patients/diseases	Treatment	Results	Side effects	Ref.
patients with stage III or IV NHL	treated with local "boost" RT at 2–50 Gy 44 patients: TBI at 0.1 Gy of X-rays/ fraction 3 times/ wk., to a total of 2.5 Gy + booster RT to slowly re-gressing masses (15–25 Gy in 2–2.5 wks); 40 patients: 8 courses of CHVmP followed by local RT (25–30 Gy in 1.5–2.0 Gy fractions)	DN FH patients were 74%, 56%, and 32%, respectively; TBI (42 evalu-able patients): CR in 15 (36 %), PR in 17 (40 %), NE in 7 (17 %) patients; CT (36 evaluable patients): CR in 20 (55 %), PR in 5 (14 %), NE in 10 (17 %) patients; ORR = 76 % for TBI and 69 % for CT patients	in TBI patients: dose-dependent TCP and leukopenia, which recovered spontaneously in the majority of cases	(Meerwaldt et al., 1991)
40 patients with stage I-IV CLL (15 received prior CT or local RT) and 41 patients with stage III-IV low grade NHL (14 with prior CT or RT)	TBI with X-rays at 0.15 Gy 2x/wk to a total of 1.5 Gy given over 5 wk followed 2 mo later by 6–9 courses of CT (prednimustine, 100 mg/m^2 orally for 5 d every 4 wk)	CLL patients: overall response rate = 85 % (91 % and 78 % in patients above and below 65 years of age, respectively): CR in 5 (12.5%) and PR in 29 (72.5%) patients (55% and 30% response rates in patients without and with pre-vious treatment, respectively); NHL patients: overall response rate = 83%: (CR in 10 (24%) and PR in 24 (58%) patients (56% and 27% response rates in patients without and with pre-vious treatment, respectively)	reversible TCP, anemia and leukopenia in 72–73% and in 50-59% of the CLL and NHL patients, respectively	(Roncadin et al., 1994)
about 200 patients with stage I and II NHL	TBI or upper HBI at 0.1 Gy or 0.15 Gy fractions of X-rays (2–3 times/wk) 15 or 10 times for 5 wk, respectively, followed by local RT at 2 Gy (5 times/ wk for 6 wks) and CT ("in most cases")	5-y survival of 84 % patients treated with TBI/HBI compared to 65 % and 70 % surviving patients treated only with local RT and with local RT combined with CT, respectively; at 9 y all 84 % patients still alive while only 50 % patients alive after local RT alone	mild and transient TCP and lymphopenia;	(Sakamoto et al., 1997; Sakamoto, 2004)
26 previously untreated patients with stage I (10 cases) and stage II (16 cases) low grade follicular NHL	TBI with of X- or γ-rays in 2 courses of 0.75 Gy in 5 fractions/wk separated by 2-wk rest followed 1 mo later by IFRT at 40 Gy in 20 fractions	after TBI only: CR in 24 (92 %) patients; after TBI + IFRT: CR in 25 (96 %) patients; 19 alive after a median of 56.2 mos with no evidence of disease	"excellent clinical tolerance" of TBI	(Richaud et al., 1998)
36 patients with high grade NHL in CR after 6–8 cycles of standard CT (CHOP)	4–6 wk after the last CHOP course TBI with γ-rays: 2 courses of 4 daily fractions of 0.2 Gy separated by 2 wks of rest (a total dose of 1.6 Gy given over 4 weeks); 4–6 wks after TBI patients with bulky disease received IFRT to initial bulky sites	3-y DFS in 61 ± 9% patients and OS in 87 ± 6% patients	transient TCP and leukopenia requiring no transfusions or growth factors; transient elevation of liver enzymes in 5 patients	(Safwat et al., 2004)
a patient with Waldenstrom's macroglobulinemia (WM) after a 6-mo course of CT (chlorambucil and prednisone)	Sept 1999: TBI with γ-rays at 0.15 Gy/ d twice weekly for ten session to total dose of 1.5 Gy	year 2003: patient asymptomatic with regards to WM	"other than transient TCP and leukopenia no acute or late side effects were noted"	(Welsh, 2004)
45 patients with metastatic melanoma	TBI at 0.1 Gy fractions of γ-rays on days 1, 8, 22, and 30; with subcutaneous IL-2; one treatment cycle included 5 weeks of treatment followed by a 2-wk break	PR in only 2 (4%), patients NE in 13 (29 %) patients, PD in 30 (67%) patients; median OS = 5.8 mos	low grade nausea in 73 %, vomiting in 68 %, fatigue in 57%, diarrhea in 43% and hypotension in 25% of patients	(Safwat et al., 2005)
58 patients with relapsed/refractory low-grade NHL (45 patients had ≥ 3 courses of CT and 40 out of 58 had "bad performance status")	2 cycles of TBI with γ-rays: 0.8 Gy/ cycle given over 4 d at 0.2 Gy/d; the cycles separated by 2-w rest (total dose of 1.6 Gy over 4 w); 4–6 wks later 20 patients additio-nally treated with IFRT to bulky sites at mean dose of 32 ± 4 Gy given at 1.8–2 Gy/ fraction, 5 times/wk	ORR = 69 %: CR in 14 (24 %), PR in 26 (45 %), SD in 12 (21 %) and PD in 6 (10 %) patients; median PFS = 14 mo, median OS = 39 mo	leukopaenia in 13 patients, anemia in 11 patients, TCP in 8 patients of median duration of 5, 9, and 12 wk, respectively	(Bayoumi and Radwan, 2015)
2 patients with prostate cancer: 1st case – a 60-y-old after extirpation of the prostate; 2nd case – a 54-y-old with inoperable end-stage cancer with bone metastases	1st patient: TBI with X-rays at 0.15 Gy once a week for 30 weeks; 2nd patient: TBI with X-rays at 0.15 Gy 3 times a week for 10 weeks + "radon sheet"[1] placed under the bed for 6 h/night for 10 months	1st patient: reduction of PSA level from >5 to 0.085 by the 6th treatment; 2nd patient: reduction of PSA level from 4.8 to 0.008 with apparent disappearance of bone metastases	NR	(Kojima et al., 2017)
patients with solid tumours: 4 patients with advanced colorectal, liver, lung, and uterine cancers with metastases (all patients pretreated with CT or local RT) and 2 patients with advanced breast cancer (a 42-year-old woman with a brain metastases without earlier treatment, and a 47-year-old woman with bone metastases diagnosed with breast	the several-week radon therapy using: a) the "radon room"[2] exposure to external γ-rays and inhalation of radon for 40 min. daily or 4 times/wk or every 2nd day (patients with breast, colorectal and uterine cancer); b) inhalation of radon from the α-Radiorespiro-Rn apparatus: 40 min. 3 times/wk or every 2nd d (patients	"regression of the disease" and/or "efficient improvement" of general conditions and laboratory tests in all patients; treatment of the patient with the hepatocellular carcinoma stopped when the cancer was "not seen even on the PET image"	no serious side effects: even after 4 mo of radon inhalation (first at 1 MBq/m^3 and then at 6 MBq/m^3) "not even minor adverse side effects emerged"	(Kojima et al., 2018, 2019)

Table 1 (*continued*)

Patients/diseases	Treatment	Results	Side effects	Ref.
cancer 5 years earlier and treated with hyperthermia)	with breast, hepacellular and lung cancer)			

Legend: AL – acute leukemia, BM – bone marrow, CHOP – cyclophosphamide, hydroxydaunoru-bicin, oncovin, and prednisone; CL – chronic leukemia, CLL – chronic lymphocytic leukemia, CML – chronic myelocytic leukemia; CNI – comprehensive lymph node irradiation; CR – complete remission (complete disappearance of all clinical, radiological, and laboratory evidence of disease); CT – chemotherapy; CHVmP – cyclophosphamide, hydroxyrubicin, Vm26, prednisone; CVP – cyclo-clophosphamide, vincristine and prednisone; d – day(s); DFS – disease-free survival; FFP – freedom from progression; FL – follicular lymphoma; GIT – gastrointestinal toxicity; HBI – half/hemi-body irradiation; HD – Hodgkin's disease; HL – histiocytic lymphoma; i.v. – intravenous; IFRT – involved-field radiotherapy; LL – lymphocytic lymphoma; ML – mixed lymphocytic-histiocytic lymphoma; mo – month/months; MPD – myelodysplastic/myeloproliferative disorder; NE – no effect; NHL – non-Hodgkin lymphoma; NR – not reported; ORR – overall remission rate; OS – overall survival; p.o. – orally; PR – partial remission; PD – progressive disease; PSA – prostate specific antigen; PTBI – protracted TBI; RT – radiotherapy; SCLC – small cell lung carcinoma; SD – stable disease; STBI – subtotal (i.e., with shielding of the skull, eyes and extremities) body irradiation; TBI – total-body irradiation; TCP – thrombocytopenia; TNI – total nodal irradiation (regional irradiation of all major lymph node areas at total doses of 20−35 Gy in daily fractions of 1.5−2 Gy for 2−4 weeks); WBC – white blood cell; wk – week/weeks; wkly – weekly; [1] "radon sheet" - a silicone sheet containing monazite and emitting radiation at about 37 μGy/h); [2] "radon room" - a small room with walls containing natural uranium ore emitting γ-rays at 11 μGy/h) and radon at the average concentration of 200 kBq/m^3; [3] α-Radiorespiro-Rn apparatus – the radon generator emitting radon at 2−6 MBq/m^3 which can be taken directly to the lungs through a suction tube.

were discontinued after the untimely death of Heublein who had become an active advocate of this type of treatment. Other investigators, however, continued testing the low-level whole-body exposures to X rays using larger numbers of patients. The results of one of such trial performed between 1931 and 1933 on 270 patients with lymphoproliferative diseases led to the conclusion that subjects who, shortly after completion of the local RT with X-rays, received between 0.5 and 0.75 Gy of whole-body X-rays irradiation – the Heublein technique – survived longer and had longer periods of remission than did patients who received only localized radiotherapy (Medinger and Craver, 1942). Between January 1941 and July 1951, Osgood, Seaman and Tivey treated 163 patients with chronic granulocytic and lymphocytic leukemia by 'titrated, regularly spaced' TBI applied in two different ways: some of the patients were given several 'spray' irradiations (i.e., spread over the entire body) from an external X-ray source at the dose of 0.1−0.2 Gy per exposure and others were internally irradiated at comparable doses from the intravenously injected radioactive phosphorus (^{32}P). The authors noted that survival of the TB-LLR-treated patients form both groups was 'significantly better than that for a collected series including all radiation treated cases reported in the literature from 1925 to 1951.' Interestingly, no difference between the clinical response to external X-ray irradiation and internal contamination with ^{32}P was noted (Osgood et al., 1955). Between 1943 and 1969 Juan Angel del Regato and co-workers, first at the Ellis Fischel Cancer Hospital of Columbia, Missouri, and then at the Penrose Cancer Hospital of Colorado Springs, for 3−7 years treated 61 patients with chronic lymphogenous leukemia to low daily doses of total-body X-rays accompanied, when required, by regional irradiation of spleen or lymph nodes (actually, del Regato had already performed a series of similar studies at the Warwick Cancer Clinic in Washington, D.C. in the late 1930s, but no reports from these studies were published due to the loss of the patients' records). The results obtained over a period from 1943 to 1969, presented for the first time by del Regato during his Janeway Lecture in 1973, indicate that a 'life-time' series of low-level X-ray irradiations resulting in the total doses ranging from 11 to 28 Gy increased the average survival of the patients to 46 months, with a maximum survival of 15 years and a 5-year survival of 21 % of the patients. Notably, 'patients who had received TBI for several years had rather healthy appearing bone marrows except for the present leukaemic infiltrates' (Del Regato, 1974).

In the 1960s several clinical programmes of TB-LLR were initiated in a number of medical institutes in the USA. One of the first was the City of Hope Medical Centre in Duarte, California, which employed a specially designed chamber to deliver whole-body irradiations with X-rays. More than fifty patients with acute and chronic leukemia, lymphoma, polycythemia vera and various types of advanced solid cancers were treated in this chamber to doses from 0.05 to 8 Gy. In this series the only group of patients in whom 'whole body irradiation was a useful adjunct' in terms of a markedly prolonged survival were the chronic leukemia patients who were irradiated at single or fractionated doses between 0.1 and 1 Gy. It is noteworthy that apart from 'some nausea or vomiting during or immediately after irradiation' at doses ≥0.4 Gy, there were 'no serious complications of the treatment program' (Jacobs and Marasso, 1965). Based on these results (as well as the parallel experience of investigators at the Medical Division of the Oak Ridge Institute of Nuclear Studies who obtained 'regression of lymphadenopathy and spleen size' in patients with lymphosarcoma and chronic lymphocytic leukemia exposed to single TBI with γ-rays at "not-really-low" doses of 0.5–1.0 Gy) (Andrews et al., 1962), Jacobs and Marasso concluded that TBI 'has some usefulness' and declared that 'this study will be continued' (Jacobs and Marasso, 1965). Meanwhile, from 1961 to 1979 over ninety patients with various haematological and solid tissue neoplasms were exposed at the Northeast Ohio Conjoint Radiation Center (NEORAD) in Hartville, Ohio, to either fractionated TBI (0.1 Gy daily to a total of 1−5 Gy) or subtotal body irradiation (STBI; 0.5 Gy daily to a total of 1−40 Gy). The results were promising: many patients with non-Hodgkin and Hodgkin lymphomas, chronic leukemias, myelomas, and seminomas had long-term ('up to 17 years or permanent') remissions of their disease. Kenneth Loeffler, the author of the review of these studies, concluded that 'STBI and TBI are useful therapeutic modalities for many of these malignancies.' (Loeffler, 1981).

In Europe, large-scale trials with TBI began in the early 1970s at the Rotterdamisch Radio-Therapeutisch Instituut (RRTI) in Rotterdam, the Netherlands (Qasim, 1975). Preliminary results obtained in stage III and IV non-Hodgkin lymphoma (NHL) patients with generalized lymphadenopathy showed that 'fractionated total body irradiation can be used safely in the management of lymphocytic lymphoma' and that this form of therapy may be 'a preferable first line method of treatment of patients with lymphocytic lymphoma' (Qasim, 1975, 1979). Hence, between 1973 and 1979, 68 patients with low to high grade NHL were treated at the RRTI with repeated low-dose TBI and the results were very encouraging: complete remissions were seen in 84 %, 42 %, and 40 % of patients with low, intermediate, and high-grade NHL, respectively. The remission rates were better in patients in whom TBI was the initial treatment than in those pretreated earlier with chemotherapy or/and standard RT (Lybeert et al., 1987). In 1975 another study was initiated in the Netherlands, this time at the Department of Radiotherapy of the University of Utrecht. In the study 30 patients with stage III and IV NHL were exposed to TBI with X-rays at 0.1 Gy per day, 3 times a week until the total dose of 3.0 Gy was reached. The best results were obtained in the 19 patients who had no previous treatment such as local RT or chemotherapy: complete remissions were seen in 53 % of such pretreated patients but as high as 77 % of the non-leukemic patients without any previous treatment (van Dijk-Milatz, 1979). At about the same time (1973–1977), 37 patients with advanced NHL, of whom 24 received no previous therapy, were treated by TBI at the Royal Marsden Hospital in Sutton, Surrey, UK. The patients were exposed ten times to

low doses of X-rays to the entire body either over 12 days (TBI) or 5 weeks (protracted TBI), or first to the most involved half of the body and 6−8 weeks later to the other half (hemibody irradiation, HBI). The overall response rate was 80 % for patients with diffuse NHL and 73 % for those with nodular lymphomas and the duration of the complete responses ranged from two to 41 months (median 12 months). HBI appeared to be the most effective and the least myelosuppressive form of treatment and the authors indicated that although their response rates were 'similar to that reported with chemotherapy' no serious toxicity was associated with HBI (Dobbs et al., 1981). Between July 1980 and November 1985 the Lymphoma Cooperative Group of the European Organization on Research and Treatment of Cancer (EORTC) conducted a randomized prospective clinical study performed in over 90 patients with stage III or IV NHL to compare the effects of low-dose TBI with those of multidrug chemotherapy combined with consolidation local RT: the overall remission rates were similar with both treatment modalities and the authors concluded that 'alternative approaches such as the use of immune response modifiers (e.g. α2 interferon) might be the next beneficial step to include in the treatment of non-Hodgkin's lymphomas.' (Meerwaldt et al., 1991). Between January 1984 and September 1992 in Italy, Mario Roncadin and his group at the Cancer Centre (*Centro di Riferimento Oncologico*) in Aviano repeatedly treated 40 patients with stage I-IV chronic lymphocytic leukemia (CLL) and 41 patients with stage III-IV low grade NHL with low doses of radiation from a 6 MV linear accelerator with excellent results: the overall response rates in the whole group of the CLL patients were 85 % (91 % and 78 % in patients above and below 65 years of age, respectively) and 83 % in the NHL group of patients (Roncadin et al., 1994). In France, Pierre Richaud and colleagues, based on the results of their earlier examination of over 100 patients with stage III and IV low-grade lymphoma who were successfully (83 % response rate) treated with low-dose TBI, from January 1986 to October 1994 evaluated the results of a similar exposure of 26 previously untreated patients with stage III and IV low-grade follicular NHL and detected complete response in 24 (92 %) of them (Richaud et al., 1998).

Similar trials were also performed in Africa. Indeed, reliable data were reported by Peter Jacobs and Helen S. King from the University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa, who in the 1980s randomly assigned 108 patients newly diagnosed with indolent lymphoproliferative diseases such as chronic lymphocytic leukemia, stage III and IV well-differentiated lymphocytic lymphoma and stage III and IV follicular lymphoma to receive either low-dose TBI with γ-rays or a two-agent chemotherapy. Although both treatment types gave comparable results in terms of complete remission rates and median survival time (59 % and 52 % and 53 and 57 months in the chemotherapy- and the TBI-treated patients, respectively), the authors highlighted two 'apparent attractions' of TBI: compared to chemotherapy, TBI led to faster ('often dramatic') resolution of the superficial lymphadenopathy and did not require as frequent monitoring of blood counts as well as the concern about failure to take medication (Jacobs and King, 1987). In view of the unsatisfactory results achieved in aggressive NHL with the standard chemotherapy (CHOP: cyclophosphamide, adriamycin, vincristine, and prednisone) and based on the earlier encouraging outcomes of a combining CHOP with TBI (Leimert et al., 1979; Weick et al., 1983) on the other side of the African continent, Akmal Safwat, Yasser Bayoumi and colleagues at the National Cancer Institute of the Cairo University aimed at testing the therapeutic efficacy of TB-LLR as an adjuvant treatment. Between September 1999 and September 2001 36 patients with high grade NHL who achieved complete remission after several cycles of CHOP were later (4−6 weeks) subjected to two courses of TB-LLR separated by two weeks of rest. The 3-year disease-free survival was 61 ± 9% and overall survival was 87 ± 6%. The authors concluded that the use of adjuvant TB-LLR in patients with aggressive NHL in complete remission after standard chemotherapy is 'a feasible, non-toxic treatment that is worthy of testing in a future phase III trial' (Safwat et al., 2004). More extensive retrospective

analysis of patients treated by TB-LLR (according to the above described regimen) at the Cairo University from 1997 to 2006 was presented by Yasser Bayoumi and Aida Radwan. In their study 58 patients with relapsed or refractory low-grade NHL were analysed (45 of these patients had ≥3 courses of standard chemotherapy and 40 had 'bad performance status'). The overall response rate was 69 %, but complete responses were seen in only 24 % and partial responses in 45 % of the patients; the median duration of progression-free survival was 14 months and the median overall survival was 39 months. The investigators concluded that the use of TB-LLR in patients with relapsed low-grade NHL is 'a feasible, effective, and tolerable treatment' worthy of further testing in combination with chemotherapy and/or targeted therapy based on specifically designed monoclonal antibodies (Bayoumi and Radwan, 2015).

In Japan, Professor Kiyohiko Sakamoto and his colleagues at the Tohoku Radiological Science Center of the Tohoku University, prompted by the results of their extensive preclinical studies carried out in the 1980s and 1990s in normal and tumour-bearing mice, initiated first clinical trials in two patients with advanced (i.e., metastasizing) tumours, one with ovarian cancer and the other with colon cancer. The tumours of the two women were surgically removed and conventional RT was locally applied. Because the diseases progressed, repeated low-dose (0.1 Gy) whole- and half-body irradiations with X-rays were also added in the first and the second women, respectively. These treatments inhibited progression of the disease in both patients (as indicated by the reduced spread of metastases) and improved their general conditions for several months. After receiving similar results in a number of other patients with advanced tumours in various organs, Sakamoto and his team embarked on a larger clinical trial in patients with NHL, a disease chosen by the investigators because of its widespread nature (i.e., neoplastic infiltration of extralymphatic sites such as bone marrow and the liver) already at the time of diagnosis. The patients were subjected to multiple half- or total-body irradiations at low-doses of X-rays followed by fractionated local RT at up to 60 Gy total dose and 'often' by chemotherapy. In about 200 patients so treated, five-year survival was 84 %. This compared favorably to 65 % and 70 % for patients treated only with local RT and with local RT combined with chemotherapy, respectively. In addition, nine years after completion of the adjuvant half- or total-body irradiations all 84 % patients were still alive compared to only 50 % patients treated only with local RT and CT (Sakamoto et al., 1997; Sakamoto, 2004). The most recent Japanese trials with TB-LLR were conducted by Shuji Kojima and his colleagues at the Tokyo University of Science in Noda-Shi, Japan. Initially, they exposed two patients with either a surgically removed or an inoperable end-stage prostate cancer with bone metastases. The first patient was whole-body exposed at low doses to X-rays 'according to the method of Sakamoto' and the second patient received similar whole-body exposures followed by a long-term 'radon sheet' treatment (for details see Table 1). Both treatments normalized the markedly elevated PSA levels in the two patients and, in the second patient, led to the apparent disappearance of multiple bone metastases (Kojima et al., 2017). In another series of experiments, Kojima and co-workers tested the effectiveness of a several-week 'radon therapy' in six patients with a breast, colorectal, lung, uterine, and hepatocellular carcinomas using a specially designed 'radon hormesis room' or the α-Radiorespiro-Rn apparatus (for details see Table 1). The disease regressed and the general condition and laboratory tests 'efficiently improved' in all the patients; in one case (hepatocellular carcinoma) the treatment was stopped when the cancer was no longer detectable 'even on the PET image.' Based on these results the authors concluded that 'radon therapy appears to be a promising treatment modality for different kinds of cancer, either as a primary therapy or as an adjuvant therapy for conventional chemotherapy and/or local high-dose radiotherapy' (Kojima et al., 2018, 2019).

4. Lessons learned

Most of the traceable/available and reliable clinical trials performed thus far which employed ultra-low dose whole-body irradiations with X- or γ-rays are reviewed in Table 1. It is clear that the design and execution of many of these trials, especially those performed in the 1940s, 1950s, and 1960s lacked the modern criteria of clinical research in terms of precise diagnosis and allocation of patients, randomization and control, blindness, clinical equipoise and other ethical issues including informed consent from and the prolonged follow-on of the patients. However, it is also clear that the amassed data from the studies performed between 1930s and 2019 provide important information which can and should be used as an encouraging foundation for future clinical trials compatible with modern criteria in which TB-LLR will be employed as a primary or additional treatment modality in hematopoietic and other malignancies. To this end, the following lessons can be learned from the hitherto performed trials:

1 Overall, from the early 1930s to the end of 2019 almost 2,000 patients were tested in systematic and individual clinical trials for the efficiency of TB-LLR. Patients with a number of different malignancies, most often advanced, were exposed to whole or half-body irradiations either as an initial (and only) treatment, as an adjuvant therapy, or as a salvage therapy. In the great majority of the trials the irradiated patients presented with lymphoproliferative diseases, predominantly non-Hodgkin lymphomas and, to a lesser extent, chronic lymphocytic leukemias. In fact, NHLs constitute about 90 % of all lymphomas and, in contrast to Hodgkin disease, their generalized character is usually present from the onset of the disease. Hence, systemic therapy rather than local irradiation of enlarged lymph nodes should be the preferred form of treatment for the majority of patients diagnosed with NHL (Johnson, 1975). Markedly less frequently were tested patients with solid tumours such as melanoma, sarcoma and colon, prostate, lung, ovarian, liver, and uterine cancers. In most cases, the radiotherapeutic protocols consisted in repeated exposures of the whole or, less frequently, half of the patient's body to X- or γ-rays administered daily at doses between 0.05 to 0.2 Gy, 2−5 times per week until a cumulative doses of 1−4 Gy have been achieved. Occasionally, after a 1−8-week rest, a similar TBI or HBI regimen was repeated. Additionally, patients with persistent nodular masses were given regional 'boost' irradiation to involved areas at total doses of 10–35 Gy applied in several daily fractions.

2 In many trials, especially in patients with NHL and in some CLL patients, exposures to low-level TBI were very encouraging. Thus, in patients with advanced stage NHL curative effects and complete remissions (CR) were obtained in 25–95 % of the cases (Qasim, 1979; Lybeert et al., 1987; van Dijk-Milatz, 1979; Dobbs et al., 1981; Meerwaldt et al., 1991; Roncadin et al., 1994; Richaud et al., 1998; Jacobs and King, 1987; Safwat et al., 2004; Johnson, 1970; Johnson et al., 1970; Johnson, 1972, 1976; Johnson, 1977; Canellos et al., 1975; Kazem, 1975; Chaffey et al., 1976; Yonkosky et al., 1978; Choi et al., 1979; Thar et al., 1979; Hoppe et al., 1981; Mendenhall et al., 1989). Intriguingly, in many of the trials best results were achieved when TB-LLR was the only or initial treatment (van Dijk-Milatz, 1979; Dobbs et al., 1981; Roncadin et al., 1994; Richaud et al., 1998; Johnson, 1972, 1976; Chaffey et al., 1976; Choi et al., 1979; Thar et al., 1979; Mendenhall et al., 1989; Chaffey et al., 1977; Carabell et al., 1979). Such exposures were also effective in patients who previously failed on or relapsed from chemotherapy (Loeffler, 1981; Lybeert et al., 1987; Dobbs et al., 1981; Bayoumi and Radwan, 2015; Yonkosky et al., 1978; Choi et al., 1979). Notably, complete remissions occurred in more than 50–60 % of the NHL patients and the less frequent, lower CR rates were detected either in patients with 'unfavorable histology' lymphomas (Mendenhall et al., 1989) or in patients previously treated with standard chemotherapy or local RT

at high doses (Roncadin et al., 1994). Generally, the efficacy of treatment was less spectacular in patients with solid cancers: while a few reports showed encouraging results (Loeffler, 1981; Kojima et al., 2017, 2018; Kojima et al., 2019; Kinsella et al., 1983) other outcomes of low-level TBI were unsatisfactory (Jacobs and Marasso, 1965; D'Angio and Evans, 1983; Safwat et al., 2005). However, most of these neoplasms were already in advanced, highly disseminated stages of growth when both the primary tumors and their metastases likely grew refractory to anti-cancer immune reactions and/or these reactions were markedly suppressed and could not be revived by low-dose irradiations.

3 In most of the trials no serious acute side effects were provoked by TB-LLR. In a minority of the cases transient 'bone marrow depression' was manifested by moderate and transient thrombocytopenia and/or lymphocytopenia and only a fraction of the patients required blood transfusion. Such outcomes were sometimes accompanied by mild and manageable nausea and vomiting occurring mostly in patients who were treated with cytotoxic therapy such as intensive chemotherapy or local high-dose RT (Jacobs and Marasso, 1965; Kazem, 1975; Kinsella et al., 1983; Rees et al., 1980). Interestingly, as reported by del Regato from his 'life-time series of X-ray irradiations' patients with CLL who received low-level whole-body irradiations for several years 'had rather healthy appearing bone marrows except for the present leukaemic infiltrates' (Del Regato, 1974). Indeed, the early studies demonstrated that absorption by the whole body of up to 25 % of a full 'erythema dose', i.e., about 7.5 Gy, delivered at the rate of approximately 5 mGy per minute is not associated with a depression in the number of white cells or an 'instance of marked drop in blood platelets' (Heublein, 1932). Likewise, two subsequent exposures of the whole bodies of patients with melanoma at 0.5–1.5 Gy of X-rays was accompanied by only 'short-lived and easily controlled' nausea and vomiting and 'a temporary leukopenia' (Holder, 1965).

Among the late complications of TB-LLR of special concern is acute leukemia, a prototypical radiogenic cancer (Modan and Lubin, 1974) the increased incidence of which has been demonstrated following treatment of various lymphoproliferative malignancies (Pedersen-Bjergaard, 1988). However, as shown in Table 1, in most of the trials no cases of secondary leukemia was detected in the followed-on NHL patients exposed earlier to repeated whole-body irradiations at low doses (Jacobs and Marasso, 1965; Lybeert et al., 1987; Choi et al., 1979; Thar et al., 1979; Hoppe et al., 1981; Mendenhall et al., 1989; Holder, 1965). Notably, even in patients exposed twice to the relatively high doses (0.5–1.5 Gy) of X-rays 'no secondary complications' were detected (Holder, 1965). Even though a few studies reported that the rates of secondary leukemias or myelodysplastic/myeloproliferative syndromes ranged from 0.5 to 8.2% among the TBI-treated NHL patients (Mendenhall et al., 1989; Carabell et al., 1979; O'Donnell et al., 1979; Greene et al., 1983; Travis et al., 1996), in all of these cases the secondary diseases developed in patients who, in addition to TB-LLR, had been exposed to high-dose local RT and/or intensive chemotherapy regimens. Noticeably, in a study where the highest (8.2 %) rate of secondary hematological malignancies (four cases of acute nonlymphocytic leukemia and one case of myelodysplastic syndrome) was diagnosed during the 15-year follow-up of the two-year NHL survivors these diseases were detected in patients who, in addition to whole-body exposures to 0.15 Gy of X rays (twice a week until the total of 1.5 Gy), received either a salvage chemotherapy with alkylating agents (1 case) or a salvage chemotherapy and localized irradiation of bulky tumour masses which delivered a median dose to the active bone marrow of 5.2 Gy (Travis et al., 1996). Indeed, excess leukemia is unlikely in populations exposed only to ionizing radiation, but it can be rather high following intense chemotherapy (O'Donnell et al., 1979; Travis et al., 1996; Gomez et al., 1982; Pedersen-Bjergaard et al., 1985). In fact, as indicated by extensive reviews of the data, prior treatment with chemotherapeutic agents

seems to be the most important risk factor for the development of sec-ondary acute myeloid leukemias in NHL patients (Ellis and Lishner, 1993; Kollmannsberger et al., 1998; Leone et al., 1999).

4 Compared to the effects of chemotherapy, which after 1948 became the accepted modality for the treatment of metastatic malignancies (Loeffler and Puterbaugh, 1975), the therapeutic effectiveness of TB-LLR appeared to be similar or better and the latter therapy has a few distinct additional advantages. During one of the first compari-sons of the two modalities conducted in 1951 at the NEORAD Center patients with various solid cancers in advanced stage were either exposed once to whole-body irradiation with X-rays at 0.4–1.5 Gy or were given a single dose of nitrogen mustard or triethylenemelamine (TEM), the two agents considered at that time as alternatives for standard radiotherapy in the treatment of cancer. The results demonstrated 'higher tolerance levels of total body irradiation' which 'may well prove of value in the management of diseases currently being treated routinely with nitrogen mustard and its de-rivatives.' Indeed, 'all patients receiving nitrogen mustard or TEM developed malaise of varying severity', but none of the patients receiving total-body irradiations reported any worsening of their condition (Loeffler et al., 1953). In August 1964, a pilot study was initiated at the Radiation Branch of the National Cancer Institute in Bethesda, MD. During the next ten years the TB-LLR treatment of patients with NHLs and chronic lymphocytic leukemia was investi-gated as an alternative to chemotherapy (Johnson, 1975; Johnson et al., 1970; Johnson, 1972; Canellos et al., 1975; Johnson, 1966, 1979; Young et al., 1977). The highly encouraging results of these trials (up to 93 % CRs in patients with advanced NHL and no clini-cally serious side effects) prompted further studies along this line. In November 1969, a group at the Harvard Medical School embarked on a programme of therapy of advanced lymphocytic lymphoma by fractionated total body exposures to X-rays (Chaffey et al., 1976; Carabell et al., 1979; Hellman et al., 1977). Complete remissions seen in 80 % of the primary treated patients, the results in substantial agreement with those obtained by Johnson et al. (1970) (Johnson et al., 1970), led the authors to opine that TBI is 'a useful alternative to combination chemotherapy since it produces comparable survival with decreased morbidity and toxicity' (Chaffey et al., 1976). Other authors who conducted similar studies in the same period of time were even more definitive by claiming that 'in terms of simplicity of treatments and morbidity, fractionated whole body irradiation is much better than combination chemotherapy' (Choi et al., 1979). A number of other tests comparing the clinical outcomes of TB-LLR with those of chemotherapy also demonstrated that the effects of the two modalities were at least equivalent and that the former treatment appeared to be less toxic, faster to resolve organ enlarge-ment, was easier to apply and control (e.g., the need for close patient follow-up was less stringent), and less likely to compromise 'the ability to tolerate future therapy'; furthermore, TB-LLR proved to be effective in patients who did not obtain remission with, or relapsed after, standard chemotherapy (van Dijk-Milatz, 1979; Dobbs et al., 1981; Meerwaldt et al., 1991; Jacobs and King, 1987; Safwat et al., 2004; Bayoumi and Radwan, 2015; Hoppe et al., 1981; Mendenhall et al., 1989; D'Angio and Evans, 1983; Hellman et al., 1977; Rostom and Peckham, 1977). These multiple results sharply contrast with the claim of Paule et al. (1985) who, based on two publications by Johnson (1979) and Rubin et al. (1981), concluded that low-dose total body irradiation 'did not appear to be superior to chemo-therapy in most trials' (authors' emphasis) and that it was associated with 'significant haematological toxicity' and 'a number of infectious complications.'

5 In view of the encouraging and, especially in case of the NHL pa-tients, even impressive results of the TB-LLR-based therapy, it is puzzling why this form of treatment has not become the standard anti-cancer strategy. The explanation is manifold. First, the

alternative modality, i.e., chemotherapy, gained ground in the late 1940s when the horrific effects of using "radiation" in the form of nuclear weapons were already well known. This has led to the adoption in the mid-1950s of the scientifically unfounded assump-tion that all exposures to ionizing radiation, no matter how small, are harmful and should be avoided (Calabrese, 2015, 2020; Marcus, 2015). This assumption, called the linear no-threshold (LNT) hy-pothesis has become the basis of radiation regulations and as such has since been inculcated into radiology and radiotherapy course participants as a binding "rule of thumb" and has significantly contributed to spreading of radiophobia not only between the gen-eral public but also among physicians and medical physicists. Indeed, to this day many medical professionals are reluctant to accept the accumulated over the last several years reliable evidence that ultra-low level irradiations are not only harmless but can also improve health (Janiak et al., 2017). It may be speculated that this reluctance is shrewdly capitalized on by pharmaceutical companies responsible for the production and supply of the many anticancer medications which more or less actively prompt systemic chemo-, immuno-, vaccine-based-, and molecular targeted therapies at the expense of generally nontoxic and less costly TB-LLR. Second, although many different mechanistic explanations of the anti-neoplastic effects of TB-LLR have been elucidated in a number of reliable experimental and pre-clinical studies, few clinical trials have thus far been aimed at similar elucidations. Consequently, most ra-diation oncologists refrain from pursuing such trials which in their opinion are not sufficiently scientifically justified.

5. Possible mechanisms

What are the mechanisms of the therapeutic effects of TBI which, especially in lymphoproliferative diseases, have been reported to pro-duce complete and/or durable remissions in 80–93 % of the patients with advanced-stage NHL? (Qasim, 1979; Lybeert et al., 1987; Richaud et al., 1998; Sakamoto et al., 1997; Johnson, 1972; Choi et al., 1979; Thar et al., 1979; Chaffey et al., 1977; Kinsella et al., 1983). As demonstrated by the many pre-clinical studies including our own ex-periments performed in radiosensitive and radioresistant mice which have been outlined in a few recent reviews (Janiak et al., 2017; Yang et al., 2016; Cui et al., 2017) stimulation of immune reactions, possibly involving a reversal of the suppressed anti-neoplastic immunity, is likely to play a critical role. Unfortunately, the immune status of patients exposed to TBI has rarely been examined, although in a few instances (see Table 1) it was demonstrated that fractionated TBI resulted in re-covery of the circulating immunoglobulin levels from subnormal to normal (Johnson, 1976), stimulated the mitogen-induced proliferation of blood lymphocytes in vitro (Yonkosky et al., 1978), increased the numbers of helper/helper-inducer T (Sakamoto et al., 1997) and NK cells (Safwat et al., 2005) and up-regulated the CD4:CD8 T cell ratio in peripheral blood (Welsh, 2004). Indirect evidence of the involvement of the immune system is provided by the earlier discussed observation that the best clinical effects of TB-LLR were seen when multiple whole-body exposures to X- or γ-rays were either the only or the first form of therapy (van Dijk-Milatz, 1979; Dobbs et al., 1981; Roncadin et al., 1994; Richaud et al., 1998; Johnson et al., 1970; Johnson, 1972, 1976; Kazem, 1975; Chaffey et al., 1976; Choi et al., 1979; Thar et al., 1979; Men-denhall et al., 1989; Chaffey et al., 1977; Carabell et al., 1979) (i.e., applied either without or before introduction of immunosuppressive, intensive chemotherapy and/or high dose radiotherapy). Indeed, as indicated by Specht in her review of the modern treatment of lym-phomas, which relies on the combination of local RT with systemic CT, 'the more intensive the chemotherapy regimen, the fewer patients benefit from radiotherapy,' even if the latter refers to irradiation of only the involved sites (Specht, 2016).

Another plausible mechanism of action of TB-LLR in patients with lymphoproliferative diseases is the low-level radiation-induced

elimination of the malignant cells (Chen and Sakai, 2004). Indeed, lymphoblasts and lymphocytes belong to the most radiosensitive cell types and, in contrast to most other somatic cells, resting lymphocytes are more sensitive to γ–radiation than their activated counterparts (Sellins and Cohen, 1987). In fact, exposure of lymphocytes to γ-rays causes an early interphase apoptotic cell death which is distinct from the mitotic, senescent, or postmitotic necrosis or apoptosis that accounts for radiation-induced cell death in most non-lymphoid malignancies (Dewey et al., 1995; Forrester et al., 2000). Intriguingly, lymphocytes are more sensitive to radiation in vivo than in vitro (Sharma et al., 2010). Consequently, lymphomas are particularly radiosensitive cancers: curative regimens of local irradiation of bulky neoplastic masses incorporate only 20–35 Gy, compared to 65 or more Gy of radiation required for definitive treatment of many solid tumours such as squamous cell carcinomas and adenocarcinomas (Kimball and Webb, 2013).

One likely mechanisms responsible for enhanced apoptosis of lymphoma cells is their hyper-radiosensitivity (HRS), a phenomenon by which radiation doses ≤0.3 Gy actually cause increased cell kill per gray, compared to higher doses (Short et al., 2001; Seth et al., 2015). Presumably, after such a low dose exposure malignant cells do not recognize the ensuing DNA damage as significant, do not initiate DNA repair, and instead choose to die an apoptotic death (Marples et al., 2004). Notably, although orderly removal of dying cells by phagocytes occurs without eliciting an inflammatory response (Fadok et al., 2001), radiation-induced apoptosis is not immunologically 'silent'. In fact, in the course of radiation-induced apoptotic death, malignant lymphoid cells express on their surface the 'eat-me' signals, such as phosphatidylserine or calreticulin, which stimulate phagocytosis of these cells and boost dendritic cells to trigger the T and NKT cell-mediated immune responses (Kimball and Webb, 2013; Fadok et al., 2001). In case of follicular lymphoma cells, irradiation induces apoptosis in these cells, while sparing macrophages, which are then activated by phosphatidylserine exposure to clear the lymphoma (Knoops et al., 2007). In fact, a patient's follicular lymphoma cells treated ex vivo with γ–radiation and loaded into dendritic cells were most effective as a cancer vaccine when high levels of calreticulin and heat shock protein 90 were expressed on the surface of the lymphoma cells (Zappasodi et al., 2010). Thus, yet another possible mechanism is the LLR-induced immunogenic cell death.

6. Conclusions and the way ahead

Results of controlled clinical trials with ultra-low dose whole- or half body irradiations with X- or γ-rays of patients with non-Hodgkin lymphomas performed from the 1960s until the late 1990s are highly encouraging: complete and durable remissions occurred in at least 50–60 % of the patients and, in some cases, the rate of remissions exceeded 90 %. Importantly, in many patients optimal results were seen when TB-LLR exposures were the only, or the initial, form of therapy. Except for moderate and transient thrombocytopenia and/or lymphocytopenia no severe acute 'toxic' effects were instigated by such treatments. Likewise, in the great majority of the trials no secondary cancers were detected in the followed NHL patients even with repeated TB-LLRs. Indeed, the few patients who developed secondary leukemia or a myelodysplastic syndrome were also treated with salvage chemotherapy and/or localized irradiation delivering high doses to the active bone marrow. Notably, the therapeutic effectiveness of low-level total-body irradiations appears to be at least similar to that of chemotherapy, the standard treatment of generalized malignancies, but surpasses the latter in lower morbidity and toxicity, faster resolution of organ tumour infiltrations, ease of application and follow-up in the immediate post-treatment period, as well as better tolerance of additional therapy. Moreover, in many cases TB-LLR proved to be effective in patients who did not obtain remission or relapsed after standard chemotherapy. Hence, as also concluded by others (Cuttler et al., 2000; Pollycove, 2007; Oakley, 2015; Block et al., 2017), ultra-low dose irradiations with X- or

γ-rays applied as a stand-alone or adjuvant treatment is likely to be superior to all the current anti-cancer modalities as it is capable of producing durable remissions with no significant side effects (Table 2).

It seems advisable, therefore, that further large scale clinical trials consistent with modern criteria are performed in patients with hematopoietic and also other systemic malignancies including, or particularly, those who are in early stages of the disease. It is critical that designs of new trials using whole- or half-body exposures to ultra-low doses of low-LET radiation envisage performing of as many as possible tests and assays aimed at elucidation of the underlying mechanisms (e. g., immunological, radiobiological, biochemical, physical etc.) of both anti-neoplastic and general condition-improving as well as conceivable untoward outcomes of such exposures. Such clinical plans will undoubtedly deepen our understanding of the biomedical effects of low-level radiation and provide evidence-based grounds for the establishment of TD-LLR as a standard anti-cancer modality.

Although combination of TB-LLR with other types of the currently used anti-cancer modalities seems a natural way ahead we are reluctant to strongly support this option. First, we are unaware of any indication from pre-clinical experiments that the effects of such a combination are superior to the effects of a single modality, especially of the sole treatment with TB-LLR. Indeed, our preliminary results indicate that concomitant whole-body irradiations with ultra-low doses of X-rays and blockade of the function of one or two immune checkpoints (with anti-CTLA-4 and/or anti-PD-1 antibodies) leads to a less, rather than more, pronounced inhibition of the growth of subcutaneously transplanted lung cancer cells than does the TB-LLR treatment used alone (unpublished). Second, as indicated by the results of many in-depth analyses all of the modern anticancer modalities, i.e., systemic chemotherapy, local radiotherapy, immunotherapy (particularly inhibition of immune checkpoints), and molecular targeted therapy are associated with a number of often serious side effects (Spain et al., 2016; Palmieri et al., 2018; Zarifa et al., 2019; Gutierrez et al., 2021). In view of the fact that there are no pre-clinical or clinical indications that ultra-low dose irradiations could protect against, reverse, or mitigate such side effects advocacy of combining TB-LLR with any of the currently used or trialed anti-neoplastic therapies seems unfounded. On the other hand, however, since low-level whole-body exposure to low-LET radiation is not likely to exacerbate untoward complications of conventional chemo- and radiotherapy, nor of any form of immunomodulatory or molecular targeted therapy, prospective recognition of plausible synergistic or additive effects of the combination of the latter with the former should not be discouraged. Specifically, addition of TB-LLR to treatment modalities that are known to bolster anti-cancer immunity, including various schemes of modern low-dose local radiotherapy (Rückert et al., 2018; Menon et al., 2019), anti-cancer vaccine-based therapy (Vermaelen, 2019) or systemic chemotherapy (Galluzzi et al., 2020) can be recommended. When combining TB-LLR with modern checkpoint inhibitors or other immunotherapies, it might be reasonable to consider the total dose selected. If, for example, we are seeking T cell mediated effects, perhaps

Table 2
Comparison of the effects of moderate and high vs. ultra-low-level exposures to ionizing radiation.

INTERMEDIATE to HIGH DOSES	ULTRA-LOW DOSES
Induce death of normal cells and damage healthy tissues	Do not induce death of normal cells and do not damage healthy tissues
May induce inflammation	Attenuate (chronic) inflammation
May suppress haematopoiesis and immune functions	Stimulate various functions of the immune system
May induce secondary cancers	Do not induce secondary cancers
Can be used only locally	As whole body exposures can be *the therapy of choice* for systemic or metastatic cancer
	Anti-neoplastic effects of whole body exposures similar to or better than those of systemic chemotherapy with lower toxicity and morbidity

the whole-body dose should be optimized to allow adequate numbers of effector cells to remain and effectively carry out the task. Similarly, the combination of low dose TBI could supplement high-dose focal therapies such as SBRT. It remains possible that such a combination of high-dose local therapy coupled with immune-stimulating TB-LLR could enhance intrinsic anti-cancer immunity but this hypothesis remains to be tested rigorously. Finally, boosting of anti-cancer immune function following removal of a bulk tumor mass by surgery seems to be a reasonable option.

In conclusion, we believe that the time is ripe for the revival of interest in and resumption of full-scale oncological applications of ultra-low level whole-body exposures to low-LET radiation in order to, as phrased by Ralph Johnson, one of the most experienced investigators in the field, "dispel the pessimism of decades over failure of treatment to alter the natural history of chronic lymphocytic leukemia" and other malignancies. Certainly, well designed and conducted randomized clinical trials with TB-LLR will likely refine and improve the efficiency of such a therapy and allow for a reliable comparison of its effects with the state-of-the-art forms of anti-cancer modalities. Indeed, it is the aim of this review to provide evidence-based grounds to allow Ethical committees to issue their approval of and encourage clinical oncologists to embark on such trials.

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CRediT authorship contribution statement

Marek K. Janiak: Conceptualization, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Mateusz Pocięgiel:** Investigation, Writing - review & editing. **James S. Welsh:** Conceptualization, Investigation, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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