

The Influence of Therapeutic Irradiation on Blood and Peripheral Lymph Lymphocytes

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Summary

This paper reviews the changes of blood and peripheral lymph lymphocytes induced by therapeutic irradiation as given for a variety of lymphoid and non-lymphoid neoplastic diseases. The irradiation brings about an abrupt reduction of the numbers of blood B and T lymphocytes. The number of lymphocytes seems to be restored within a few months after irradiation, while at least 3-5 years appear to pass before the number of blood T lymphocytes is restored. The pattern of recovery seems to be the same whether the thymus has been included in the field of irradiation or not. In the adult organism, considerable differences apparently exist between the capacities for reproduction of B and T lymphocytes.

The number of lymphocytes in peripheral lymph is also much reduced in the irradiated patient and remains so for a long period. This is compatible with the concept that migration from blood to peripheral lymph is a feature quite specific for T lymphocytes.

These results are discussed in relation to the immune defense against infection and autologous tumor, and also in relation to the influence of radiotherapy on the immune defect in Hodgkin's disease.

Convincing evidence now exists that therapeutic irradiation including large blood vessels, brings about peripheral blood lymphocytopenia (1-7) (fig. 1). Similar effects are found after extracorporeal irradiation of peripheral blood (8-10), and it seems reasonable to assume that the blood lymphocytopenia induced by irradiation for cancer, is brought about mainly by irradiation of the blood itself (6). It remains unknown to what degree the blood lymphocytopenia is influenced by irradiation of lymphocytes reciding in lymphatics and lymphoid tissue within the field of irradiation.

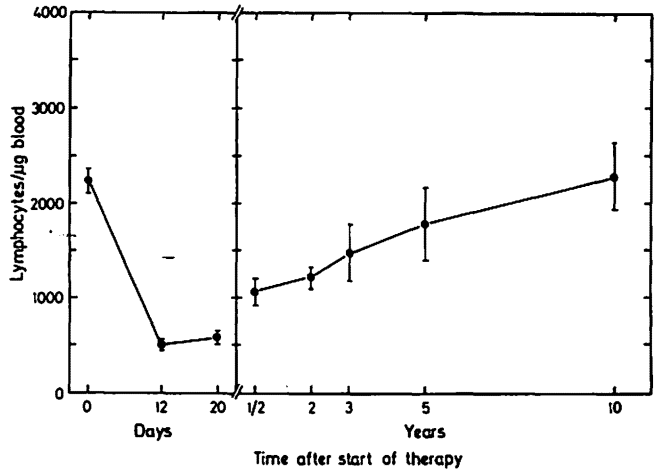
There are at least two subpopulations of blood lymphocytes. B lymphocytes have immunoglobulin molecules in their cell membrane and may be detected by fluorescent anti-immunoglobulin (11). T lymphocytes will form spontaneous, non-immune rosettes with sheep

erythrocytes (12, 13). T lymphocytes have also been measured by their ability to transform into blasts upon contact with the mitogen phytohemagglutinin (14, 15). Some workers hold that during the irradiation period, a more grave reduction is induced of the number of blood B than of T lymphocytes (4-6), while others have found an equal reduction of both subpopulations (15). This may possibly depend on methodological differences. Some results suggest that a relatively radioresistant blood lymphocyte subpopulation is left behind, consisting mainly of T lymphocytes (6). This subpopulation awaits further characterization.

After therapeutic irradiation, the total number of blood lymphocytes is gradually restored (fig. 1). However, major differences appear to exist between the recovery rates of the numbers of blood B and T lymphocytes. While the number of B lymphocytes has been recorded as normal at intervals of 3-36 months after irradiation (6, 7, 15, 16), the number of T lymphocytes remains consistently depressed at three years. At five years, the number of T lymphocytes may be normal again (6, 17).

The slow recovery of blood T lymphocytes suggests that the net production of T lymphocytes is quite low in the adult organism. Since the pattern of recovery appears to be the same whether the thymus has been included in the irradiation: whether the thymus has been included in the irradiation field or not (6, 7, 15), it may be that most of the new T lymphocytes are produced outside the thymus. Experimental evidence indicates, however, that the thymus is repopulated within 4 weeks from local single-dose irradiation of 30 Gy (18). Whether this is followed by a second phase of atrophy of the gland after months or years, is not clear, but it may well be that the thymus can produce new

Fig. 1 Mean total number of blood lymphocytes \pm 1 SD during (left part of figure) and after (right part of figure) irradiation of the iliacal and paraaortic lymph nodes with 40 Gy for seminoma testis. Left part of figure includes data from 17 patients, while the right part is based on 5 groups of patients irradiated 1/2–10 years previously. These groups each included 5–7 patients. From (6).



Leucocyte number per mm^3 peripheral lymph in patients with small carcinomas and lymphomas.

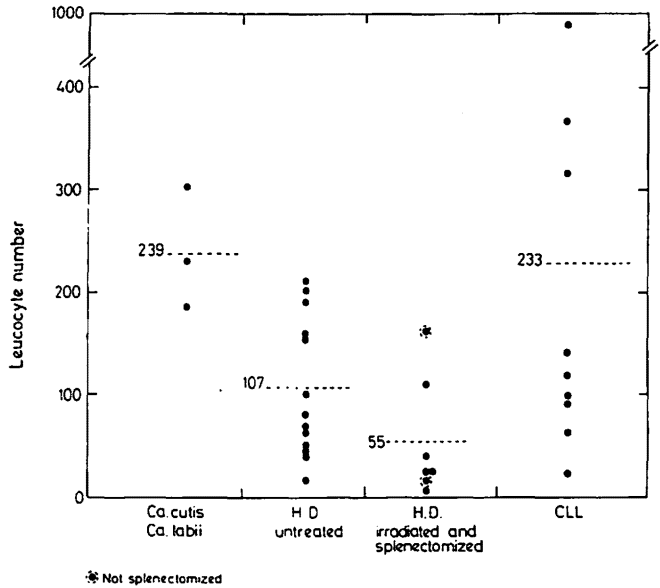


Fig. 2 Leucocyte number per mm^3 of peripheral lymph in patients with small carcinomas and lymphomas. H.D. = Hodgkin's disease. CLL = Chronic lymphocytic leukemia. From (16).

T lymphocytes after local irradiation doses of 30–40 Gy. A local irradiation dose of 15 Gy to the thymus does not give significant atrophy after one year in the rat (18). Thus the site of formation of new blood T lymphocytes after therapeutic irradiation of adult individuals has not been defined.

Since the number of blood B lymphocytes recovers much more rapidly than that of blood T lymphocytes, the adult organism probably

has a greater capacity for production of new B than for T lymphocytes. Available evidence indicates that the bone marrow is of prime importance for the development of B lymphocytes in mammals (19). After local irradiation at doses of 40 Gy, the bone marrow undergoes depopulation and atrophy, but new active bone marrow develops quite rapidly in non-irradiated parts of the skeleton (20). Thus the production capacity for new B lymphocytes

may be well retained after therapeutic irradiation.

Since deprivation of lymphocytes from peripheral blood is followed by a restoration of both main subpopulations of lymphocytes, although at different rates, regulatory mechanisms must exist that can induce net new productions of both subpopulations. Their nature remains unknown.

Available data indicate that therapeutic irradiation brings about a lymphocytopenia also in peripheral lymph, which will recover only slowly (16). This can be easily explained if one assumes that mainly T lymphocytes migrate from blood to peripheral lymph. This assumption seems natural since in patients with chronic lymphocytic leukemia with blood B lymphocytosis, the number of lymphocytes in peripheral lymph is similar to that found in other cancer diseases (16, 21), and the number of B lymphocytes in the lymph is low (21). Data presented at this symposium suggest that the migration process is highly specific for a subset of T lymphocytes with Ia determinants on their surface (22). If this can be confirmed, the relations between this subset and the possible, radioresistant subset of T lymphocytes should also be elucidated.

Prolonged extracorporeal irradiation of blood leads to prolonged survival of transplanted allografts (23). Therapeutic irradiation for Hodgkin's disease has been shown to induce cutaneous anergy to dinitrochlorobenzene (DNCB), (24), and the data would suggest that both the primary and secondary immune response are affected. Therapeutic irradiation therefore appears to reduce or, possibly, delay the reactivity of the T lymphocyte system. It is tempting to propose that this is due to a low number of T lymphocytes in tissue fluid.

No report seems to suggest that patients irradiated for cancer testis, mammary carcinoma or other non-lymphoid, solid tumors have increased susceptibility to infection during the recovery period. Important functions of all parts of the immune system therefore must remain intact after the irradiation procedure, despite the prolonged T lymphocytopenia in

blood and peripheral lymph. This may in part be explained by repopulation of irradiated lymphoid tissue. When irradiation is applied locally to lymph nodes, they are depopulated of lymphoid cells, but complete repopulation then takes place, even after a single dose of 30 Gy (25). The output of cells from the lymph node is also rapidly restored (26). Afterwards, the lymph node undergoes atrophy (27, 28), but it remains populated by lymphoid cells and may react to antigenic stimuli (27). Thus therapeutic irradiation does not destroy completely the immune function of irradiated lymph nodes. A second factor to be considered, is the difference of radiosensitivity between the primary and the secondary immune response (29). The mean total dose received by the circulating lymphocyte pool, is probably well below the dose needed to destroy the secondary immune response (6), and it may well be that enough circulating lymphocytes are given so little irradiation as to retain to some degree also the primary immune response. The hypothesis should be considered, however, that the immune defect following therapeutic irradiation is more pronounced for the primary than for the secondary immune response. Whether or not differences of immune reactivity may exist between the drainage fields of irradiated and unirradiated lymph nodes, remains to be studied. Thirdly, the relatively rapid restoration of the number of blood B lymphocytes is probably of prime importance for the defence against a number of infectious agents.

In malignant lymphoma, especially Hodgkin's disease, the situation may appear somewhat different. It has been amply documented that the incidence of infections during the course of malignant lymphoma, at least Hodgkin's disease, is higher than in non-lymphoid malignancies (30-32). Available evidence fails to suggest that therapeutic irradiation induces other changes of blood lymphocytes in Hodgkin's disease than in similarly treated cancers, e.g. testicular cancers (6, 33). Although these data are somewhat preliminary, and although studies of lymph lymphocytes in other cancers are lacking after radiotherapy, it would seem rational to suggest that the susceptibility to infection in Hodgkin's disease is not caused by

radiotherapy. A debate still goes on if blood T lymphocytes from patients with Hodgkin's disease display a specific reduction of their immune reactivity (34, 35). It could also be that the cause of this disease feature should be sought among monocytes or the non-circulating cells of the lymphoreticular system.

Since the secondary immune response probably remains relatively intact after the period of irradiation, and since the immune reactivity of the local lymph nodes are not completely destroyed, it would seem natural to presume that the host immune response to autologous, malignant tumor also remains competent. Therapeutic irradiation would therefore probably not affect adversely the prognosis in cancer, despite its effect on blood and peripheral lymph T lymphocytes and its acute depopulation of lymphoid tissue. Available evidence now clearly supports this hypothesis (36, 37). The results suggest, though, that therapeutic irradiation may lead to an increased frequency of distant metastases. Whether or not this is due to immune mechanisms, is still unknown. The filtering capacity of the irradiated lymph node is known to be reduced (27), and this may possibly enhance the spread of the malignant cells.

Blood lymphocytopenia is a feature met with in many chronic diseases, both of neoplastic and non-neoplastic nature (38). Available evidence suggests that at least in cancer, this lymphocytopenia is mainly one of T lymphocytes (34). In Hodgkin's disease a correlation has been found between the blood lymphocyte number and cutaneous delayed hypersensitivity in untreated patients (39). Similar studies are lacking for non-lymphoid cancers and non-neoplastic diseases, but if such a correlation can be found even there, the lymphocytopenia of non-irradiated patients with chronic diseases bears close similarities to that encountered during the recovery after therapeutic irradiation. It is not known if the blood lymphocytopenia in non-irradiated chronic disease is caused by increased consumption, decreased production and/or redistribution of recirculating lymphocytes, but it might be taken to reflect the same low capacity of the adult organism

to produce new T lymphocytes as has been found after radiotherapy.

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