CLINICAL TOLERANCE IN LARGE FIELD RADIOTHERAPY – THE KNOWLEDGE GAINED OVER THE LAST TEN YEARS

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ABSTRACT
Malignant disorders are still far from being successfully managed in spite of the apparent progress achieved by surgical treatment, high energy radiotherapy (RT) and chemotherapy (CHT). They keep being the second most frequent cause of lethal outcomes both in Bulgaria and in most countries of the world.

One of the promising approaches to increasing the efficaciousness of treatment is development and use of methods that are in full accord with the modern requirements of a complex therapy. Over the last fifty years, large field radiation techniques, applied as systemic therapy in oncology, have been investigated and established. These techniques show the transition in oncology to using actively various variants of large field radiotherapy (LFR), the “heavy artillery” of oncoradiologic practice, as an alternative or adjunct therapy to chemotherapy (CHT).

In the present paper we review the current knowledge in the field and present the clinical experience accumulated over the last ten years with respect to clinical tolerance in the major large-field radiotherapy techniques – total body irradiation, half body irradiation, whole abdominal irradiation, total and partial lymphoid irradiation.

Described in detail are the contemporary knowledge about clinical and hematologic tolerance in total body irradiation as part of the myelo- and nonmyeloablative conditioning regimens as well as in half body irradiation as a systemic therapy in oncology. We also present the amassed experience in clinical tolerance in partial body irradiation in the form of whole abdominal and total or partial lymphoid irradiation.

Another point worth noting based again on the experience gained over the last ten years is that for LFR we need to develop a radiotherapy technique that is designed carefully to achieve an optimal therapeutic effect that should include the disease control, good clinical tolerance and reduction of post-radiotherapy sequelae.

Key words: large field radiotherapy (LFR), total body irradiation (TBI), half body irradiation (HBI), whole abdominal irradiation (WAI), total lymphoid irradiation (TLI) and partial lymphoid irradiation (PLI), clinical tolerance (CT)

INTRODUCTION

Despite the obvious progress in the treatment of malignant diseases as a result of surgery, high energy radiotherapy (RT) and chemotherapy (CHT) there is still much to be desired for in terms of successful management of these disorders. They have been estimated to be the second most frequent cause of death both in Bulgaria and in most countries worldwide. Besides their high recurrence rate, the reason for this is mostly the refractory occult hematogenous and lymphogenous metastases that are unsuccessfully treated. Successful management of these disorders with a radical or palliative purpose is still a crucial criterion for the efficiency of a given therapeutic modality.

One of the promising approaches to increasing the efficaciousness of treatment is development and use of methods that are in full accord with the modern requirements of a complex therapy. Over the last fifty years, large field radiation techniques, applied as systemic therapy in oncology, have been investigated and established. This has
become possible because of the considerable clinical experience amassed in oncology, the advance of radiobiological knowledge, the improvement of radiotherapy equipment and the development of clinical dosimetry.

In Bulgarian radiological practice the term “systemic radiotherapy” (SRT) appeared in the 90s of last century. It showed that oncology moved towards active use of different types of large field radiotherapy, the “heavy artillery” of oncoradiologic practice, as alternative or adjunct treatment to chemotherapy. As a radiotherapeutic modality LFR is much more rarely performed in the routine clinical practice than local irradiation which is why collecting enough clinical material for research is difficult and often takes several decades to carry out. In addition you have to possess a lot of knowledge in the field, considerable clinical experience and a sense of responsibility in order to administer this type of treatment.

The aim of the present review is to present the state-of-the-art in the knowledge in this field and the clinical experience accumulated over the last 10 years with respect to the clinical tolerance in the major large-field radiotherapy techniques – total body irradiation, half body irradiation, whole abdominal irradiation, total and partial lymphoid irradiation.

CLINICAL TOLERANCE IN LARGE FIELD RADIO-THERAPY

CLINICAL TOLERANCE IN TOTAL BODY IRRADIATION

Over the last decade, total body irradiation (TBI) has been established as a basic component of conditioning regimens in allogeneic and autologous bone marrow transplantation (BMT) in patients at high risk of leukemias, lymphomas, autoimmune disorders, and some solid tumors. Clinical tolerance in the myeloablative regimens, including high dose TBI with a total dose of 9 – 15 Gy delivered prior to BMT is still a subject of scientific interest.1,2 The standard premedication recommended now by modern researchers includes antiemetics, glucocorticoids and adequate hydration before irradiation. After TBI transitory elevation of the number of granulocytes and decrease of the number of lymphocytes are observed in the peripheral blood count. Dramatically raised are the serum levels of cortisol, adrenocorticotropic hormone, the inflammatory proteins as well as the levels of interleukin 6 and the tumor-necrosis factor. Their elevation is associated with the activation of the hypothalamus-hypophysis axis.3

The main symptoms are transitory nausea and vomiting, stomatitis, enteritis, alopecia, erythema or eruption and diarrhea which, according to the majority of modern authors, are moderate and controllable.1,3 They all can be managed by applying some aggressive therapeutic activities. Vasomotor reactions such as headache, rhinitis, dizziness, and mild parotitis for several days, stomatitis and vulvitis may be observed in part of the patients. Mucosal and gastrointestinal reactions are the most pronounced with less than 10% of the patients developing high-grade early toxicity.4

More serious complications are the development of interstitial pneumonitis, hemorrhagic cystitis, and heart reactions including pericarditis, veno-occlusive liver disease or infections which result from the achieved immunosuppression. One serious side effect of TBI is radiation pneumonitis.5 Its occurrence depends on the dose and dose rate as well as on patient’s age. According to Schneider et al. in patients < 16 years it is recommended to reduce the lung dose to 11 Gy.5 Although uncommon the already developed forms of radiation pneumonitis still remain difficult for treatment and are most often fatal.

Of particular interest is the development of early and chronic reaction of the transplant against the recipient, the so called Graft versus Host Disease (GvHD).6,7 The frequency of chronic GvHD varies from 20% in the full donor-recipient compatibility to 40% in cases of partial compatibility.8 Cutler et al. reported of 59.1% of chronic GvHD in 83 patients subjected to a regimen including cyclophosphamide and TBI.7 The major risk factors for the development of chronic GvHD proved to be: the presence of already developed early GvHD, malignant hematologic disease, a female donor to a male recipient, application of TBI as a part of the conditioning regimen, donor’s age ≥ 50 years, recipient’s age > 10 years.7

When high dose TBI is carried out it is also confirmed that there is a higher risk of loss of hearing and vision and development of persistent pains in patients.8 Gurney et al. report about such painful symptoms in 2% of 235 patients who were transplanted by them, and about 36% frequency of cataract developed 15 years after transplantation.8

Certain thyroid problems, growth disorders and development of secondary malignancy after application of myeloablative conditioning regimens with included TBI, are also subject of intensive study.9 Researchers report that the thyroid dysfunction-free
survival rate is 73.2% at 5 years and 59.2% at 10 years in 153 patients with leukemias subjected to TBI.10

Early and late renal toxicity are another subject of scientific interest for the oncoradiologic community.1 Confirmed main risk factors for the development of early renal toxicity are the primary disease itself, previous drug toxicity, TBI, previous renal dysfunction, veno-occlusive disease, sepsis, dehydration and partial donor-recipient compatibility. According to Esiashvili N et al. in children subjected to myeloablative conditioning regimens including TBI, early renal toxicity reaches 45%, and late toxicity - 25% at the end of the first year after transplantation.1 The great majority of authors consider that dose size does not affect significantly the development of renal toxicity.1

The analysis of Cheng et al. (including 12 clinical studies of a total of 1,108 patients subjected to 24 different conditioning regimens of TBI and CHT) shows that there is dose dependence of late renal toxicity on the TBI performed.11 Drug treatment has also an effect on the renal function and may modify the observed dose-response correlation.11 Fractionation of the dose and dose rate may also affect the development of renal toxicity in patients subjected to TBI and BMT.

The frequency of hemorrhagic cystitis mainly associated with high doses of cyclophosphamide was strongly reduced by taking urometexan (mesna) and intensified hydration. The routine application of antiepileptic drugs in patients receiving high doses of busulfan also resulted in reduced frequency of grand-mal seizures. It is also confirmed that patients who receive grafts from compatible donors demonstrate better clinical tolerance than those with alternative graft sources.

Life threatening reactions and complications are observed in less than 20% of the patients. The conditioning regimen-related mortality is usually 15%-25% in the standard regimens which are used in young patients in remission.2

Modern authors report that in TBI increased doses > 14 Gy do not result in better therapeutic outcomes but significantly worsen the clinical tolerance.12 The frequency of early GvHD and the 2-year treatment-related mortality in TBI with 14 Gy and 15.6 Gy are related respectively 18%-36% and 20%-33%.12

It is well known that the clinical tolerance in the nonmyeloablative conditioning regimens is significantly better compared to the conventional ones. Severe mucositis, veno-occlusive disease and other life threatening reactions and sequelae are of significantly smaller frequency. Infectious complications, which are a major problem in the post transplantation period, are more rarely observed and that is associated with the presence of a host’s own hemopoiesis. The development of Cytomegalovirus infection is significantly delayed in patients subjected to nonmyeloablative BMT, but the overall one-year frequency is comparable to the one with the conventional regimens. This makes it necessary to perform a follow up 100 days after BMT which is similar to the one in patients subjected to conventional treatment. The frequency of early and chronic GvHD does not differ significantly from the one of the conventional regimens.

Recent retrospective studies report of 10% to 13% frequency of secondary neoplasm developed 15 years after TBI and CHT.13 It has a wide spectrum that includes non Hodgkin’s lymphoma, myelodysplastic syndrome, skin, head and neck tumors and other solid tumors. The advanced age of patients and the immunosuppressive therapy against chronic GvHD correlate significantly with the development of secondary neoplasm.

However, it is particularly optimistic that long-survivors after TBI are most often in an excellent health status like the ones subjected to a conventional CHT treatment.

CLINICAL TOLERANCE IN HALF BODY IRRADIATION

Clinical tolerance in half body irradiation (HBI) is also well examined and in its essence does not differ significantly from the one in TBI. Clinical studies of the last decade on the role of HBI as a systemic and palliative treatment contribute to its evaluation.14-18

Premedication is not usually applied. The physician also can give antiemetics, glucocorticoids and adequate hydration may be prescribed before irradiation. Modern authors confirm what was claimed earlier that high dose HBI is well tolerated especially when it is applied as adjuvant treatment.14-18

Well known is the reaction of blood count to HBI which leads to the conclusion that bone marrow is capable of bringing to sufficient repopulation.17,18 Four hours after radiation leucocytosis is determined in the hemogram (the so called abortive elevation), and it is observed up to the 24th hour. Immediately after that the leucocytes fall down and a depressive phase sets in. Recovery may occur after two weeks. Leucocytosis is caused by the mobilization of the marginal pool of granulocytes while the lymphocytes
disappear from blood without preceding elevation. Critical levels are not reached. Both hemoglobin and hematocrit show insignificant reactions. Hemo-

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and 23 months after the treatment. A Canadian National study on 257 patients with early ovarian carcinomas, subjected to WAI, melphalan treatment or intraperitoneal installations of $^{32}$P, reported the development of a secondary neoplasm in 29 (11%) of the patients.

**Clinical Tolerance in Total and Partial Lymphoid Irradiation**

Partial body irradiation in the form of total or partial lymphoid irradiation, the so-called extended field technique, which is applied in Hodgkin’s disease (HD) and in non-Hodgkin’s lymphomas (NHL), has well studied clinical tolerance. The scientific interest in its evaluation continues to exist in last decade.

Well known are the acute radiation reactions like occipital alopecia, mild skin reactions, dry cough, altered taste, dysphagia, reflux, emesis and rarely diarrhea which appear after LFR in HD and NHL and depend on the applied radiotherapeutic technique.

Some side effects, unpleasant and uncomfortable for the human organism, like vomiting, mucositis or neutropenia are fully controllable by the help of the contemporary supporting therapeutic activities. Other side effects are permanent; they persist long after the performance of the chemo- and radiotherapy and even after the primary oncologic disorder is healed. Hematologic toxicity is one of them. Ha et al. found recovery of hemoglobin, leucocytes and thrombocytes within 3 years after the performance of total lymphoid irradiation. The multivariate analysis of the authors shows that only patient’s age has significant influence on thrombocyte recovery.

According to modern authors early toxicity is considerably higher in older patients after the performance of extended field technique. According to Klimm et al. early toxicity in older patients depends on the applied LFT and is in proportions 26.5%:8.6% respectively for the extended field or the involved field technique.

Late toxicity and cancerogenesis after extended field technique were also studied during the recent years. It is well known that some organs like the lung, liver, testes or the ovaria have limited capacity to recover after radiation and they can not be included into the radiated fields without subsequent impact on their functions. For example, radiation pneumonitis develops within 6 to 12 weeks after completion of the Mantle technique. The risk of its development is associated with the radiated volume, the daily and the total dose. The probability to develop it increases with the parallel application of bleomycin. In precisely elaborated Mantle technique radiation pericarditis develops in less than 5% of the patients. It is especially important to differentiate this syndrome from recurrent HD. Lhermitte’s syndrome appears in 10 to 5% of the patients, usually 1 to 2 months after the Mantle technique is completed and disappears spontaneously after 2 to 6 months. Significant xerostomia develops after radiation of the Waldeyer’s ring. Subclinical hypothyroidism, a common late reaction, is developed in less than half of the patients with HD. Particularly important and serious complication is sepsis which is developed after splenectomy or radiation of the spleen. Attention must be paid to the reproductive organs too. If no adequate protection is ensured for men, radiation of the pelvis is followed by azoospermy which is most often transitory. Reactions to radiation in women depend on the age of the patient. Even in precisely performed oophoropexy and well planned RT, the scattered radiation is enough to influence the ovarian function and to cause menopausal symptoms in female patients over 30 years, while in the younger ones that effect is not observed. Combined therapeutic programs which include CHT и RT, may influence the menstrual function and fertility even in young women.

Literature analysis shows that HD is the most common primary onc hematologic disorder in which the development of hematologic and secondary solid malignant neoplasm is observed. Acute myeloid leukemia, myelodysplastic syndrome, NHL and solid tumors are prevailing. The last meta-analysis carried out on 3,221 patients of 19 clinical studies does not report statistically significant differences regarding cancerogenesis after the performance of extended or involved field RT ($p = 0.28$). Breast cancer however is significantly more frequent after extended field RT ($p = 0.04$).

**Conclusions**

In the recent three decades the interest to the application of in the treatment of different life threatening hematologic and lymphoproliferative disorders and solid tumors is determined by the necessity to find out some therapeutic approaches which are alternative to CHT and must possess definite cancericidal potency and systemic anti tumor effect.

The accumulated clinical experience of the recent decade, including also innovative radiotherapeutic techniques in the routine practice, shows that in
LFR it is necessary to elaborate a well deliberated radiotherapeutic technique aiming to achieve an optimal therapeutic effect which includes control over the disease as well as assuring of a good clinical tolerance and reduction of the radiotherapeutic sequelae.

REFERENCES


КЛИНИЧЕСКАЯ ПЕРЕНОСИМОСТЬ ПРИ БОЛЬШЕПОЛЕВОЙ РАДИОТЕРАПИИ – ПОЗНАНИЯ ПОСЛЕДНЕГО ДЕСЯТИЛЕТИЯ. ЛИТЕРАТУРНЫЙ ОБЗОР
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РЕЗЮМЕ
Результаты лучеэффективности эндометриальной возможностей методов лечения, равно как и возможность применения высокоэнергийных онкологических центров, обеспечиваемых в современных условиях, являются основой для разработки новых методов лечения.

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Одно из перспективных направлений повыше-
Обсуждается и накопленный опыт в области клинической переносимости при частичном облучении тела в форме полного облучения брюшной полости и толстых или частичного лимфоидного облучения.

Накопленный за последнее десятилетие клинический опыт показывает, что при БПР необходимо разработать хорошо обдуманную радиотерапевтическую технику в целях достижения оптимального терапевтического эффекта, включающего как контроль за заболеванием, так и обеспечение хорошего клинического толеранса и редуцирование радиотерапевтических последствий.