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ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic

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The International Lymphoma Radiation Oncology Group (ILROG) guidelines for using radiation therapy (RT) in hematological malignancies are widely used in many countries. The emergency situation created by the COVID-19 pandemic may result in limitations of treatment resources. Furthermore, in recognition of the need to also reduce the exposure of patients and staff to potential infection with COVID-19, the ILROG task force has made recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments. The guidance is informed by adhering to acceptable radiobiological parameters and clinical tolerability. The options for delaying or omitting RT in some hematological categories are also discussed. (Blood. 2020;135(21):1829-1832)

Background

The COVID-19 pandemic has created an unprecedented challenge for health care systems worldwide.1,2 Radiation therapy (RT) is regarded as essential in many clinical circumstances and must be provided even during these difficult times. Yet, limitations in resources, including space, equipment, and staff, may result in reduction of treatment capacity. Furthermore, exposure of high-risk patients should be minimized by limiting the number of visits for RT.

General guidelines on RT under these conditions have been issued by several organizations. However, special considerations are pertinent for RT of hematological malignancies. The International Lymphoma Radiation Oncology Group (ILROG) is a well-recognized worldwide organization of radiation oncologists with a record of producing guidelines for modern RT of these diseases that have become standard.3-13 With the present guidelines, ILROG aims to help radiation oncologists treating hematological malignancies make rational choices regarding possible changes to reduce the pressure on RT institutions in the current emergency situation. With regard to treatment techniques, keeping those with which the staff is familiar is recommended. Simpler techniques are encouraged when resources are limited.

Strategies

There are 3 potential strategies to reduce the demand for RT during the pandemic: omitting, delaying, and shortening the RT course. There are also clinical situations in which RT can be used as a bridging measure, resulting in rapid and effective tumor control, delaying the need to initiate systemic therapy. To decide on the most appropriate action in patients with hematologic malignancies, clinicians need to carefully assess disease factors (indication for radiotherapy, expected benefit, and natural history of disease) and patients’ individual risk in case of COVID-19 infection (age, comorbidities, and expected case-fatality rate).

Omitting RT

When the risk of severe outcomes from COVID-19 infection (for those aged ≥60 years and/or with serious underlying health conditions) outweighs the benefit of RT, omitting RT is to be considered in the following situations14,15:

- in a palliative setting, where alternatives can be offered (eg, optimizing pain control);
- for localized low-grade lymphomas if completely excised (eg, follicular lymphoma, marginal zone lymphoma, cutaneous B-cell lymphoma)13;
- for localized nodular lymphocyte-predominant Hodgkin lymphoma if completely excised16; and
- in consolidation RT for diffuse large B-cell lymphoma/ aggressive non-Hodgkin lymphoma (NHL) in patients who have completed a full chemotherapy course and achieved a complete remission.
Table 1. Standard and proposed emergency fractionation schemes for curative and palliative RT for hematologic malignancies

|                  | Standard                  | Emergency COVID-19 crisis alternative dose fractionation | BED calculations, Gy |
|------------------|---------------------------|--------------------------------------------------------|----------------------|
|                  | Total dose, Gy | No. of fractions | Comments | Total dose, Gy | No. of fractions | Dose/Fraction, Gy* | EQD2 α/β = 3 Gy | EQD2 α/β = 10 Gy |
| Curative         |                           |                           |          |               |               |                        |                      |                     |
| HL favorable, chemo-sensitive | 20 | 10 | Consider hypofractionation only in a critical resource shortage situation | 18 | 6 | 3 | 22 | 20 |
| HL unfavorable, chemo-sensitive | 30.6 | 17 | Consider hypofractionation only in a critical resource shortage situation | 27 | 9 | 3 | 32 | 29 |
| NLPHL RT alone  | 40 | 20 | Consider hypofractionation only in a critical resource shortage situation | 36-39 | 12-13 | 3 | 43-47 | 39.42 |
| HL, chemorefractory disease | 40-50 | 20-25 | No significant cardiac and/or lung exposure and no overlapping critical organs | 30 | 6 | 5 | 48 | 38 |
| Aggressive NHL, chemosensitive | 30 | 15 | No significant cardiac and/or lung exposure and no overlapping critical organs | 25 | 5 | 5 | 40 | 32 |
| Aggressive NHL, chemorefractory disease | 40-50 | 20-25 | No significant cardiac and/or lung exposure and no overlapping critical organs | 30 | 6 | 5 | 48 | 38 |
| Localized aggressive NHL, primary RT alone (not chemo candidate) | 24 | 12 | Start with 4 Gy ×1, reevaluate after 2-3 mo→ If insufficient response, proceed to definitive RT | 4 | 1 | 4 | 6 | 5 |
| Indolent lymphoma, limited stage | 45† | 25 | In patients treated with effective chemotherapy regimen† | 36 | 9 | 4 | 50 | 42 |
| Cutaneous T-cell lymphoma, TSEBT | 10-12 | 6-10 | Give 2-3 treatments, 1 per week, evaluate response after each | 8-12 | 2-3 | 4 | 11-17 | 9-14 |
| Solitary bone plasmacytoma or solitary extramedullary plasmacytoma | 40-45 | 20-25 | Nonspine, non-H&N sites | 30 | 6 | 5 | 48 | 38 |
|                  |                           |                           | Spine or H&N sites | 36 | 12 | 3 | 43 | 39 |

BED, biological equivalent dose; chemo, chemotherapy; CNS, central nervous system; EQD2, equivalent dose in 2-Gy fractions; H&N, head and neck; HL, Hodgkin lymphoma; NK, natural killer; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; TSEBT, total skin electron beam therapy.

*When using 5 Gy per fraction to 25 to 30 Gy or 4 Gy per fraction to 36 Gy, we recommend keeping the maximum dose (Dmax) to ≤25 Gy for retina, optic nerves, optic chiasm, cochlea, brainstem, brachial plexus, spinal cord, and cauda; V25 (the volume of the organ receiving 25 Gy) <5 cc for stomach, duodenum, and other small bowel; mean liver dose <20 Gy; and mean dose <6 Gy for kidney (bilateral, but optimal if 1 kidney can be spared). If these dose constraints cannot be met, we recommend using 3 Gy per fraction to 27 Gy for chemosensitive disease and 36 Gy for chemorefractory disease.

†With optimal chemotherapy.

†In patients who are not treated with chemotherapy, or in those treated with nonoptimal regimens, a higher effective dose is needed, and use of the standard fractionation should be considered if at all possible.
The fractionation sensitivity of hematologic malignancies is underreported in clinical series. However, laboratory data suggest little to no shoulder on the linear-quadratic model of cell survival, leading to a large value of $\alpha/\beta$. We therefore expect the biological effect of radiation on lymphoma cells, measured as equivalent dose in 2-Gy fractions (EQD2) to lie between EQD2 using $\alpha/\beta = 3$ Gy and EQD2 = total dose.

The suggested hypofractionated schemes have little reduction of the total dose aiming to maintain the same level of tumor control. The risks of acute and late toxicity to normal tissues associated with large dose per fraction and higher EQD2 for $\alpha/\beta = 3$ Gy are currently mitigated by the use of modern conformal RT techniques. Modern technology offers steep dose gradients around the target tumor with most of the surrounding normal tissues in the low-dose volume. Hence, if possible, using technology that provides optimal conformality is even more important here, including good quality control and daily image guidance. The risks are also mitigated by the low RT doses used in hematological malignancies, particularly the indolent types.

The accuracy of the prediction of the $\alpha/\beta$ model may be less for the larger fraction sizes. Therefore, to mitigate clinical risk, we have used dose-per-fractionation regimens that many in the clinical community are already familiar with and know are well tolerated.
Hypofractionation has, however, not been rigorously tested in prospective randomized trials in the curative treatment of hematologic malignancies, and, therefore, the treatment schedules proposed are recommended to apply only to the emergency situation of the COVID-19 pandemic. For patients with substantial cardiac or lung exposure, standard (2-Gy) fractionation should be used if at all possible.

In Table 1, we present guidelines for possible abbreviated fractionation schemes for different clinical presentations that could be used in an emergency like the present COVID-19 pandemic. Other fractionation schemes could also be appropriate, depending on clinical circumstances, if the EQD2 is equivalent to curative standard treatment regimens. We have included guidance for constraints for doses to normal tissues, but it is important to note that the proposed abbreviated treatments should always be used with due consideration and clinical judgment in individual cases.

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REFERENCES
1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [published online ahead of print 24 February 2020]. JAMA. doi:10.1001/jama.2020.2648.
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-337.
3. Constine LS, Yahalom J, Ng AK, et al. The role of radiation therapy in patients with relapsed or refractory Hodgkin lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018;100(5):1100-1118.
4. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines [published correction appears in Blood. 2019;133(12):1384-1385]. Blood. 2018;132(16):1635-1646.
5. Dabaja BS, Specht L, Yahalom J. Lymphoblastic lymphoma: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2018;102(3):508-514.
6. Illidge T, Specht L, Yahalom J, et al. International Lymphoma Radiation Oncology Group. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018;102(2):314-319.
7. Ng AK, Yahalom J, Gods J, et al. Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89(4):854-862.
8. Specht L, Yahalom J, Illidge T, et al; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89(4):854-862.
9. Tsang RW, Campbell BA, Gods J, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the International Lymphoma Radiation Oncology Group (published correction appears in Int J Radiat Oncol Biol Phys. 2018;102(5):1602). Int J Radiat Oncol Biol Phys. 2018;101(4):794-808.
10. Yahalom J, Illidge T, Specht L, et al; International Lymphoma Radiation Oncology Group. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2015;92(1):11-31.
11. Bakst RL, Dabaja BS, Specht LK, Yahalom J. Use of radiation in extramedullary leukemia/ chloroma: guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018;102(2):314-319.
12. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in central nervous system leukemia: guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018;102(1):53-58.
13. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2015;92(1):32-39.
14. National Comprehensive Cancer Network (NCCN). B-cell lymphomas. 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2 January 2020.
15. National Comprehensive Cancer Network (NCCN). Primary cutaneous lymphoma. 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2 January 2020.
16. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children’s Oncology Group. J Clin Oncol. 2016;34(20):2372-2379.
17. Aldridge DR, Radford IR. Explaining differences in sensitivity to killing by ionizing radiation between human lymphoid cell lines. Cancer Res. 1998;58(13):2817-2824.
18. Bentzen SM, Dör W, Gahlbauer R, et al. Bioeffect modeling and equeffective dose concepts in radiation oncology-terminology, quantities and units. Radiother Oncol. 2012;105(2):262-268.

Footnotes
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