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Immunotherapy and Radiotherapy for Older Cancer Patients during the COVID-19 Era: Proposed Paradigm by the International Geriatric Radiotherapy Group

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Abstract

Background: Older cancer patients with locally advanced or metastatic disease may benefit from chemotherapy alone or combined with radiotherapy. However, chemotherapy is often omitted either because of physician bias or because of its underlying comorbidity, thus compromising their survival. The coronavirus disease 19 (COVID-19) pandemic is compounding this issue because of the fear of immunosuppression induced by chemotherapy on the elderly which makes them more vulnerable to the virus. ***Summary:*** Immunotherapy has less effect on the patient bone marrow compared to chemotherapy. The potential synergy between radiotherapy and immunotherapy may improve local control and survival for older patients with selected cancer. Preliminary data are encouraging because of better survival and local control in diseases which are traditionally resistant to radiotherapy and chemotherapy such as melanoma and renal cell carcinoma. ***Key Message:*** We propose a new paradigm combining immunotherapy at a reduced dose and/or extended dosing intervals and hypofractionated radiotherapy for older patients with selected cancer which needs to be tested in future clinical trials.

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Introduction

Management of older cancer patients remains a challenge because of their frailty and underlying comorbidity [1]. However, even for fit older cancer patients, chemotherapy, when indicated, is often denied because of their chronological age [2].

Physicians are often reluctant to initiate systemic therapy because of the fear of immunosuppression which may lead to severe debilitation from treatment complications [3]. The advent of coronavirus disease 19 (COVID-19) further compounded the issue as infected older patients are more likely to die compared to younger patients who become infected [4–6]. Infected individuals may be asymptomatic leading to inadvertent chemotherapy for those patients unless diagnostic testing for the virus becomes widely available. However, delaying chemotherapy during this pandemic is likely to result in poorer survival for those patients [7]. Thus, systemic therapy that spares the bone marrow may be a reasonable alternative. Currently, many biologic agents such as tyrosine kinase inhibitors may be effective and exert less toxicity on the aging bone marrow [8]. One of the systemic treatment options, immunotherapy, is particularly intriguing because of its potential synergy with radiotherapy [9]. The abscopal effect of radiotherapy at higher doses has been reported in many case reports [10–12]. Hypofractionation is frequently advocated during the COVID-19 pandemic to shorten treatment time, decrease treatment cost, and decrease the risk of exposure to the virus for cancer patients. Thus, the combination of immunotherapy and radiotherapy may be an attractive concept to improve survival and quality of life for older cancer patients during this uncertain time. As an international organization devoted to the care of older cancer patients, women, and minority, the International Geriatric Radiotherapy Group (http://www.igrg.org) [13] would like to take the initiative to recommend an innovative treatment to that population who is often discriminated. This review examines the preliminary data reporting the possible beneficial effect of immunotherapy and radiotherapy and proposes a new paradigm for the management of older cancer patients during the COVID-19 era.

Physiology of Bone Marrow Aging

In animal experiments, aging is associated with an increased accumulation of fatty acids associated with increased inflammatory cytokines such as interleukin 7, tumor necrosis factor, and interferon-gamma in the bone marrow [14, 15]. The metabolic changes observed parallel a decrease of leucocytes and lymphocytes. Interestingly, chemotherapy given to young mice also produces a similar pattern suggesting that chemotherapy accelerates the aging process of those animals [15]. Even though the mechanism of bone marrow aging in humans remains unknown, current evidence suggests a chronic state of inflammation in older patients, leading to increased fatty cells in their bone marrow [16]. Paradoxically, the number of hematological stem cells (HSCs) also increased but their function to generate normal bone marrow cells decreased with age which may explain chronic anemia in older patients [17]. Indeed, in a study of 1,714 normal individuals of both sexes, compared to younger people, older patients had a significant increase in serum proinflammatory cytokines such as interleukin-6, interleukin-18, and C-reactive protein [18]. As a result of this chronic inflammation, the prevalence of anemia increases rapidly after the age of 50 to a rate of over 20% for individuals who are 85 years old or older [19]. A significant rate of mortality up to 35% has been reported among older adults with anemia compared to the ones without [20]. Other studies also corroborated the impact of anemia on mortality and frailty of older patients [21, 22]. Thus, any treatment intervention that further depresses the bone marrow of those patients is likely to increase mortality risk.

Impact of Chemotherapy on Bone Marrow Function

Chemotherapy has been reported to induce acute and long-term suppression of the bone marrow. Permanent damage and long-term suppression of HSCs were observed following repeated exposure of various chemotherapeutic agents [23]. Damage to those HSCs was dose-dependent and increased significantly at high dose leading to bone marrow failure and potential death [24, 25]. Even though the data are scarce because of the exclusion of older cancer patients in most prospective studies, among older breast cancer patients physically fit to be enrolled in clinical trials, a higher rate of grade 4 hematologic toxicity was observed compared to younger patients following chemotherapy [26]. Those who were frail had a higher risk of death compared to the ones without. Survival rates were 22 and 55%, respectively, for metastatic older breast cancer patients receiving chemotherapy with and without comorbidity [27]. This high rate of serious hematologic toxicity among older cancer patients receiving chemotherapy was also corroborated in other studies [28, 29] and may

explain in part the reluctance of physicians to recommend chemotherapy for older cancer patients [30]. However, omitting or delaying chemotherapy because of the fear of toxicity may compromise their survival [31]. A possible alternative solution to this conundrum is to find a systemic therapy that is effective, yet carrying less toxicity to the bone marrow for those patients.

Potential of Immunotherapy as an Effective Systemic Agent in Lieu of Chemotherapy for Older Cancer Patients

In selected patients, immunotherapy has an advantage over conventional chemotherapy. It targets the immune system specifically, thus decreasing the frequency of grade 3–4 hematologic toxicity even though in rare cases the immune response may cause normal organs' damage. As an illustration of immunotherapy safety, in a meta-analysis of 9,234 cancer patients receiving checkpoint inhibitors (CPIs), the prevalence of neutropenia was only 0.9% [32]. In addition, boosting the immune system may allow it to adapt to the cancer cells when they underwent changes to escape detection. Long-term survival may be achieved through immune memory. A variety of immunotherapy strategies has been introduced such as targeted antibodies, cancer vaccines, adoptive cell transfer, and CPIs with various success rates and toxicity profiles. As an illustration of immunotherapy specificity, in cancer of the bone marrow such as multiple myeloma, who had recurred following at least 2 lines of therapy including autologous stem cell transplant, Daratumumab, a monoclonal antibody targeting CD38-expressing tumor cells, produced a 38% response rate and improved progression-free survival among those patients who responded. Grade 3-4 hematologic toxicity was acceptable in that study (5%) [33]. A particularly attractive form of immunotherapy, CPIs, has been advocated because of preliminary report of synergistic effect with radiotherapy [10–12]. Cancer cells can escape the body immune surveillance system through the PD1/PD-L1 pathways which prevent CD4+ T lymphocytes from recognizing them. By blocking that pathway, CPIs allow T lymphocytes to recognize tumor cells and to initiate the immune system to destroy them [34]. Thus, local control may be improved. Radiotherapy may enhance the immune response through a complex mechanism which involves many processes from stimulation of dendritic cells to enhancing migration and function of CD8+ T lymphocytes responsible for killing tumor cells [9]. This systemic effect of radiotherapy away from the local irradiated tumor volume is referred to as an abscopal effect [35]. Even though the abscopal effect of radiotherapy has been historically reported a long time ago, its revival is promoted because of its synergistic effect with immunotherapy. Concurrent immunotherapy and radiotherapy may potentially improve local control and survival compared to immunotherapy alone. As hypofractionated radiotherapy has been recently advocated to reduce treatment time for older cancer patients and to decrease their risk of exposure to COVID-19, this radiotherapy fractionation may also increase tumor control if combined with immunotherapy [13]. Randomized trials of hypofractionated radiotherapy compared to conventional fractionation have reported similar survival and complication rates in various solid tumors such as breast and prostate cancer [36, 37].

Therapeutic Effect of Immunotherapy Compared to Conventional Chemotherapy in the General Cancer Population

Preliminary data on immunotherapy have been very promising for various tumors. A meta-analysis of advanced urothelial carcinoma treated with pembrolizumab monotherapy versus platinum-based chemotherapy reported a 12-month survival rate of 41 and 30%, respectively [38]. A similar meta-analysis of CPIs compared to chemotherapy for advanced non-small cell lung cancer (NSCLC) demonstrated a significant improvement of survival and progression-free survival among patients treated with CPIs. There was also a significant reduction of grade 3–4 adverse events [38]. The survival improvement was most pronounced for patients who had tumors expressing a high PD-L1 proportion score of >50% [39]. In chemoresistant tumors such as melanoma where chemotherapy was proven not only ineffective but also associated with significant side effects, CPIs have been reported to improve survival with acceptable complications [40]. A randomized study of nivolumab compared to standard chemotherapy for recurrent head and neck cancer also demonstrated superior survival and significant reduction of grade 3–4 side effects in patients receiving nivolumab [41]. Another study on a different CPI, pembrolizumab, also corroborated this survival benefit and less toxicity compared to chemotherapy for those patients [42]. Thus, taking together, those randomized studies illustrated the survival improvement and safety profile of CPIs compared to chemotherapy for selected solid tumors.

Efficacy and Safety Profile of Immunotherapy in Older Cancer Patients

A systemic analysis of CPI efficacy reported the similar survival between older cancer patients (65 years old or older) and younger patients who had advanced or metastatic solid tumors [43]. The safety profile of CPIs was also corroborated in another study [44]. Interestingly, in one study looking specifically at the efficacy of immunotherapy between older and younger patients, the response rate was statistically higher for older NSCLC patients [45]. The response rate was, respectively, 30.8 and 10.5% for older and younger patients despite a significantly higher proportion of advanced disease in the older group. Furthermore, preliminary dose reduction studies of CPIs reported a similar survival compared to full dose [46, 47]. As an illustration, in a study comparing the full dose of nivolumab and pembrolizumab to a lower dose based on patient weight and body mass index in patients with metastatic cancer, there was no difference in survival between those two groups [48]. In addition, there was no difference in tumor control for patients with locally advanced NSCLC treated with pembrolizumab with dose ranging from 2 to 10 mg/kg or with nivolumab between doses of 3 and 10 mg/kg [49, 50]. The low clearance and long half-lives of CPIs may explain their efficacy for tumor control even with a reduced dose. As an alternative to dose reduction, extended dosing intervals for CPIs may be another attractive option for older cancer patients because of their difficulty in transportation and their risk of exposure to pathogens such as COVID-19. The Food and Drug Agency (FDA) recently approved pembrolizumab 400 mg every 6 weeks instead of 10 mg/kg every 2 weeks [51].

Other investigators also proposed a further reduction of pembrolizumab dose at 4 mg/kg capped at 400 mg every 6 weeks to reduce treatment cost based on the drug pharmacokinetics [52]. Thus, dose reduction and/or extended dosing intervals of CPIs appear to be viable options for older cancer patients and need to be investigated in future prospective studies.

Efficacy of Immunotherapy and Radiotherapy for Solid Tumors

Even though the data are still preliminary, the combination of immunotherapy and radiotherapy seems very promising. For example, advanced melanoma which has been traditionally resistant to both radiotherapy and chemotherapy had a significant response to both immunotherapy and radiotherapy compared to immunotherapy alone. Durable responses were observed among those receiving the combined treatment without increased toxicity [53]. Objective response rate was higher among patients receiving CPIs and radiotherapy [54]. Even though the study included a small number of patients and was retrospective, it highlighted the potential benefit of the combined modality which was also corroborated in subsequent studies. As an illustration, the complete response rate was, respectively, 25.7 and 6.5% for immunotherapy concurrently with radiotherapy and immunotherapy alone. In addition, improved survival was also observed among patients who received the combined treatment [55]. Two meta-analyses also confirmed the safety and survival benefit when high-dose radiotherapy such as stereotactic ablative radiotherapy (SABR) was added to immunotherapy compared to SABR alone confirming the synergistic effect of those two modalities [56, 57].

In patients who underwent palliative radiotherapy and concurrent immunotherapy with nivolumab for metastatic cancer, a higher survival and progression-free survival were observed among patients receiving a higher radiation dose compared to a low dose. As radiotherapy should not have any impact on survival in metastatic cancer patients because it is a local treatment, the study suggested that higher radiation dose may lead to a better immunotherapy response which ultimately resulted in a better survival [58]. Even though the study was limited because of the small number of patients, it highlighted the impact of high radiation dose on survival benefit observed when SABR was combined with immunotherapy [56, 57]. However, there was concern that concurrent immunotherapy and radiotherapy may increase toxicity and may negate the survival benefit for patients who had brain metastases. Central nervous system toxicity and the presence of blood-brain barrier to CPIs may impair treatment response.

The safety of CPIs was confirmed in a study combining immunotherapy with whole brain radiotherapy or stereotactic radiosurgery (SRS) for NSCLC brain metastases [59]. In another study of 1,104 patients who had brain metastases from melanoma, the addition of CPIs to SRS significantly improved survival compared to SRS alone. The median survival was 11.1 and 6.2 months, respectively, for the combined modality and SRS alone [60]. There was no difference in toxicity when CPIs were added to SRS. This survival benefit of CPIs and SRS for brain metastases of various solid tumors was also corroborated in other studies [61, 62]. Adding CPIs to SRS may delay or decrease the incidence of new brain metastases which

may have accounted for the improvement in survival [60]. This observation also mirrored the importance of SRS in similar studies where SRS was added to TKI to improve survival in patients who had brain metastases [63]. Thus, CPIs may improve survival of patients with advanced or metastatic solid tumors with reduced toxicity compared to chemotherapy. Indeed, two recent review articles highlighted the synergy between CPIs and radiotherapy and provided the details of their interaction [64, 65].

As most of the older cancer patients are frequently excluded from clinical trials, there is a paucity of data assessing efficacy and toxicity of CPIs and concurrent radiotherapy. However, in one study, older patients (75 years old or older) with brain metastases did not seem to have worse survival compared to younger patients [66]. Anecdotal evidence suggests that long-term survival and complete response were possible for those patients when nivolumab was added to radiotherapy [67]. Stereotactic body radiotherapy which is frequently used to treat older cancer patients with early-stage NSCLC because of coexisting morbidity seemed to be safe when combined with CPIs [68]. However, prospective studies are needed to confirm this hypothesis.

In this era of COVID-19, treatment of older cancer patients remains a challenge because of their poor survival if infected and the presence of comorbidity. Preliminary evidence suggests that cancer patients who received immunotherapy were not likely to contract COVID-19 compared to matched controls. Among 1,577 patients receiving immunotherapy, 21 (1.3%) tested positive to the virus compared with 527 out of 26,241 patients for the matched control (2%) [69]. Conversely, cancer patients who were treated with immunotherapy and got infected with the virus during treatment did not seem to have a higher mortality rate compared to the cancer population [70]. Forty-nine out of 113 patients (43%) continued to receive CPIs despite the infection. Thus, immunotherapy seemed to be safe during the pandemic. However, more prospective studies need to be carried out to assess the safety of immunotherapy for those patients before any definitive conclusion. As the viral clinical manifestations may be indistinguishable from CPI complications, it may be safer to withhold immunotherapy until the patient is cleared of the infection.

Standard chemotherapy regimens depress their bone marrow and expose them to viral infection. Thus, a new paradigm needs to be developed for those patients. We propose CPIs at a reduced dose and/or at extended dosing intervals combined with hypofractionated radiotherapy for older patients with selected locally advanced or metastatic cancer. For patients who have lung cancer, CPI dose reduction may also reduce the risk of significant pneumonitis associated both modalities compared to full dose but need to be corroborated in future prospective studies. As an international research group with a large network of over 1,100 cancer institutions in 126 countries, the IGRG can conduct those studies to assess their impact on quality of life and survival of older cancer patients.

Conclusion

Immunotherapy because of its different toxicity profile may be better tolerated and more effective compared to standard chemotherapy for older patients with selected cancer such as lung cancer. Hypofractionated radiotherapy combined with immunotherapy is an attractive concept because of its potential abscopal effect. Immunotherapy is safe and effective for older cancer patients. A reduced immunotherapy dose and hypofractionated radiotherapy should be considered for older patients with selected cancer in future prospective studies to assess its impact on patient quality of life in an era where chemotherapy may expose them to the lethal effect of viral infection.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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