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The Impact of KEYNOTE-522 Related Immune-Related Adverse Events on Concurrent Adjuvant Whole Breast Radiotherapy in the Real World: A Case Series

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ABSTRACT

Background: In the KEYNOTE-522 study, a phase III, placebo-controlled trial, stage II-III triple negative breast cancer (TNBC) patients were randomized to receive neoadjuvant pembrolizumab versus placebo, plus paclitaxel and carboplatin for 4 cycles, followed by pembrolizumab versus placebo, plus cyclophosphamide and doxorubicin or epirubicin for 4 cycles. Adjuvant radiotherapy with standard fractionation was delivered concurrently to adjuvant pembrolizumab or 2 weeks before it. No information on irradiated volumes, modalities, or radiotherapy interruption duration was reported. Hypofractionated radiotherapy is the standard treatment, but it was not allowed in this study. Thus, published safety data do not comply with real-world practice.

Case presentation: We present a case series of 2 consecutive TNBC patients developing acute toxicity during adjuvant moderate hypofractionated radiotherapy concomitant with pembrolizumab due to severe immune-related adverse events (irAEs). Both patients stopped adjuvant RT definitively.

Conclusion: In KEYNOTE-522, the impact of irAEs on the RT adjuvant treatment was underestimated. In the real world, the occurrence of irAEs during radiotherapy should be taken into account, raising the question about the timing of hypofractionated radiotherapy with new long-course systemic therapy.

INTRODUCTION

During the past 20 years, several novelties have been introduced in breast cancer adjuvant treatments. First of all, schedules of whole breast radiotherapy (RT) have been shortened into moderate or ultra-hypofractionated RT. In fact, 16-, 15-, and 5-fraction schedules have been adopted according to the most important high-quality randomized trials like START trials A-B[1,2], Ontario trial[3], Danish trial[4], FAST-Forward[5], and YO-HAI5 trials.[6] As a result, several benefits have been recorded: the same outcomes in terms of local control and toxicity with conventional schedule, reduced waiting lists, and easy access to RT

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facilities. Thus, moderate and ultra-hypofractionated RT have been accepted as standard schedules in lieu of the conventional fractionation using the 2 Gy/fr regimen. Since 2018, ASTRO guidelines have recommended the use of hypofractionated RT for all breast cancer, regardless of grade and phenotype.[7] Systemic treatment has also evolved from first- to third-generation chemotherapy combinations. Moreover, the introduction of immune checkpoint inhibitors has revolutionized the fate of patients affected by triple-negative breast cancer (TNBC). In this regard, the KEYNOTE-522 trial should be considered an important practice-changing study.[8] By this trial, patients with stage II-III TNBC were randomized to receive neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab after surgery, resulting in significantly longer event-free survival than neoadjuvant chemotherapy alone. Data on estimated EFS at 36 months and overall survival at 60 months were up to 80 % in this group, with statistical significance. Adverse events such as immune-related adverse events (irAEs) were consistent with the established safety profiles of pembrolizumab and chemotherapy.[9] Hypofractionated RT trials have also been practice-chancing trials since they have demonstrated equivalent outcomes with standard fractionation and advantages in terms of RT facilities access and waiting lists.[7] Thus, it is considered a standard worldwide. However, it is also noteworthy that hypofractionated RT was not allowed in the KEYNOTE-522 trial. In fact, all patients received standard fractionated RT, and 114 out of 1174 patients had RT concurrent with pembrolizumab. irAEs events were recorded in the KEYNOTE-522 trial in both phases, but little information were provided on the impact of irAEs on RT interruptions was provided. Several pieces of real-world evidence on a few patients with this schedule are in line with the toxicity data reported by the study, assuming a safe profile of this combination without relevant interruption of radiotherapy. Although these reports are encouraging, herein we present data on 2 consecutive triple negative patients developing severe acute toxicity due to irAEs during adjuvant hypofractionated RT concomitant to pembrolizumab, causing definitive interruption of the adjuvant radiotherapy delivery. No further RT was added. Patients entered into a strict follow-up program to evaluate how this RT interruption could influence the disease relapse or overall survival next.

Case 1

A 56-year-old woman affected by triple-negative left breast cancer T2 N1, after induction of pembrolizumab plus chemotherapy, underwent a conservative surgery. The final specimen revealed a complete pathological response. Thus, she started adjuvant pembrolizumab concurrent with adjuvant RT. She received adjuvant RT to the left breast with a hypofractionated regimen of 2.67 Gy/40.05 Gy with Intensity-Modulated Radiation Therapy (IMRT) and breath-hold (BH) technique. Concomitant pembrolizumab second cycle was delivered during the tenth fraction of RT. Three days later, she developed acute skin erythema, which spread to the whole body, followed by pruritus and extensive desquamation (Figures 1 and 2). Steroids and anti-H2 were supplied for more than 10 days. She stopped RT definitively at 11 out of 15 fractions of RT.

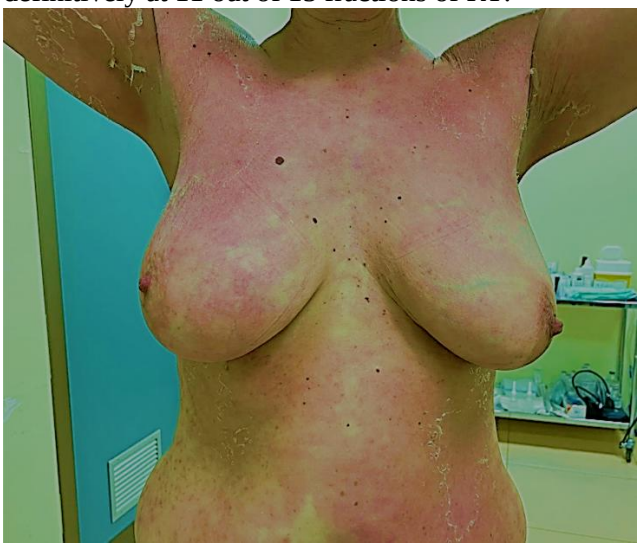

Figure 1. Diffuse Erythema Spread to the Whole Body

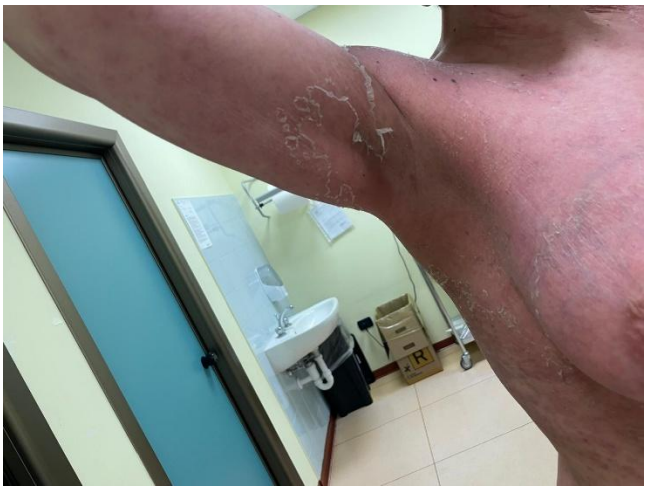

Figure 2. Erythema with Desquamation

Case 2

A 45-year-old woman with triple negative T2 N0 in the right breast was treated with induction pembrolizumab plus chemotherapy, followed by a conservative surgery. The specimen showed a complete pathological response. She started maintenance pembrolizumab concomitant with RT. She received adjuvant RT on the right breast with a

hypofractionated regimen of 2.67 Gy/40.05 Gy with a 3D conformal RT technique. The first cycle of concomitant pembrolizumab was delivered the day before RT. Five days later, she developed febrile neutropenia with coughing. Chest CT scan showed bilateral ground glass opacities (Figure 3).

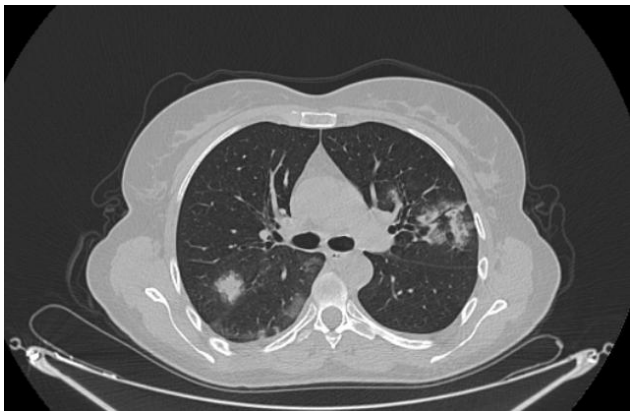

Figure 3. Pneumonia with Bilateral Diffuse Ground Glass Opacities

She stopped RT with 5 out of 15 fractions. After receiving steroids, the clinical symptoms ameliorated after 2 weeks. CT scan showed a complete resolution of the pneumonia (Figure 4). Thus, she stopped RT definitively.

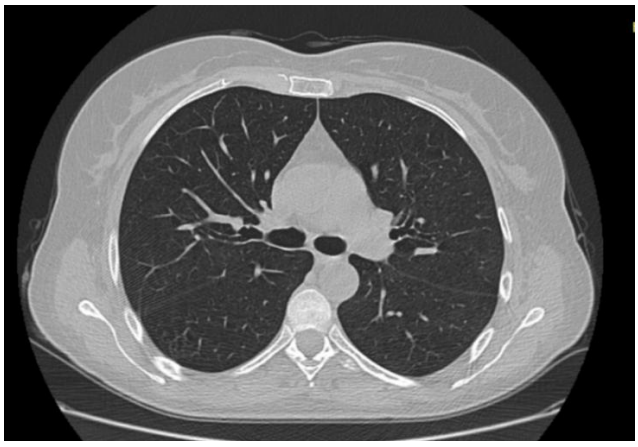

Figure 4. Resolution After Therapy

DISCUSSION

The results of the KEYNOTE-522 trial, which randomly assigned 602 previously untreated stage II or III TNBC patients to receive standard neoadjuvant chemotherapy with anthracyclines, carboplatin, and taxanes plus pembrolizumab or placebo, showed a significant increase in a complete pathological response with neoadjuvant chemotherapy when combined with immunotherapy. Prompted by this strong evidence, international guidelines now recommend pembrolizumab plus chemotherapy as a new standard of care in stage II and III TNBC. In regard to RT, the original KEYNOTE-522 study protocol initially did not permit concurrent RT with pembrolizumab. Later, through an amendment, only 144 out of 1174 patients received concurrent adjuvant pembrolizumab with RT.[8,9] Interestingly, locoregional treatment-related adverse events reported during the neoadjuvant phase were similar or higher than those recorded during the adjuvant phase with radiotherapy: 4.4% versus 1% severe skin reaction, 1.3% versus 1.3% pneumonitis, and 0.4% versus 0% myocarditis rates for the experimental and control arms, respectively. Thus, pembrolizumab concurrent with RT was considered safe, but from a radiation oncologist's point of view, several considerations need to be taken into account, as suggested by Alcom *et al.* in a commentary.[10] Safety results were not stratified by receipt of concurrent or sequential RT, nor were the details of radiation therapy in terms of irradiated volumes, techniques, or days of RT interruptions due to irAEs reported. Moreover, patients were treated with standard fractionated RT which nowadays has been replaced by moderately or ultra-hypofractionated RT worldwide. Thus, it is out of date to use the conventional long course 2 Gy/fr in daily clinical practice even with this protocol.

Several pieces of real-world evidence adopting adjuvant whole breast RT with moderately hypofractionated schedules concurrent with pembrolizumab are available. The existing data seem to confirm the safety of this combination minimizing the role of irAEs in the delay or interruption of RT. In a comparative nonparametric study, Myers *et al.* reported on 139 women treated with neoadjuvant pembrolizumab plus chemotherapy (RT+P) according to the KEYNOTE-522 regimen, with 287 consecutive patients who received neoadjuvant chemotherapy alone. Experiencing ≥1 irAE was associated with delayed radiation ($P = 0.029$).[11] Tison *et al.* reported a real-life experience on 28 patients treated with RT and concurrent pembrolizumab and 27 patients treated with RT alone. RT schedules were 50 Gy in 25 fractions of 2 Gy for the chest wall with or without nodal RT. For breast RT, 40.05 Gy in 15 fractions of 2.67 Gy with sequential 16 Gy or 48 Gy in a simultaneous boost was allowed. A dose of 50.4 Gy in 28 fractions of 1.8 Gy was prescribed to the chest wall; whole breast or regional nodal irradiation was performed. In this case, a 64.4 simultaneous-integrated boost was provided. As a result, no differences were observed between the RT+P and the RT only groups. During RT, no patients experienced acute or late grade 4 to 5 adverse events. In the RT+P group, 1 patient experienced G3 breast pain, while in the RT-only group, 1 patient had grade 3 radiodermatitis.[12] Colciago *et al.* in a recent preliminary report on 10 patients treated with the

KEYNOTE-522 regimen with moderately hypofractionated Volumetric Modulated Arc Therapy (VMAT) and IMRT, detected a very low rate of severe irAEs during the RT time. Interestingly, pneumonia, breast pain, or neutropenia did not occur while the most notable local side effect was G2 radiodermatitis, noted in 2 patients. Two patients experienced severe systemic toxicities requiring a definitive interruption of radiotherapy.[13] It is well-acknowledged how in RT delivery, gaps and interruptions bring about a negative impact on local control.[14]

Our patients treated with the KEYNOTE-522 regimen during RT developed severe adverse events leading to a definitive interruption of adjuvant RT. These events raise questions on the timing of adjuvant RT in these patients to avoid RT discontinuation when irAEs occur. Given our previous experience on hypofractionated RT upfront to long-course adjuvant RT, it is reasonable to provide the same timing with adjuvant pembrolizumab with ultra-hypofractionated RT.[15] The rationale is that high-dose per fraction RT is able to modulate the tumor microenvironment, thus enhancing an immune-antitumor effect inside and outside the radiation field.[16] By preclinical data in a low immunogenicity mouse model of TNBC, RT upregulated the expression of genes containing immunogenic mutations.[17] Moreover, a multicenter phase 2 study evaluated the effectiveness and safety of combined radiotherapy and pembrolizumab in metastatic TNBC patients. The study found that in the intention-to-treat cohort, the objective response rate (ORR) of the unselected programmed death-ligand 1 (PD-L1) population was 17.6%; this was higher than that of metastatic TNBC patients who had previously received immune checkpoint inhibitor monotherapy.[18] Thus, the upfront timing of hypofractionated RT before Pembrolizumab needs to be explored.

CONCLUSION

The KEYNOTE-522 phase III trial has revolutionized the curative prospective of stage II or stage III TNBC. Data on safety in the pembrolizumab concurrent RT are in line with the literature reported on thoracic irradiation combined with pembrolizumab for lung cancer, as assessed by a meta-analysis of 3652 articles of NSCLC treated with immunotherapy. [19] In addition, in a multidisciplinary consensus of European Society for Radiotherapy and Oncology with regard to the combination of new drugs with radiotherapy, 95% of the experts agreed on the concurrent delivery of pembrolizumab and RT.[20] Up to now, moderate and ultra-hypofractionated RT has been the standard treatment over the conventional one applied in KEYNOTE - 522. Thus, the impact of irAEs on adjuvant whole breast hypofractionated RT discontinuation needs to be assessed and solved. The use of upfront hypofractionated RT could be a valid option.

ETHICAL CONSIDERATIONS

The patients were fully informed about the details of their disease being presented in this journal, and both signed an informed consent form.

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CONFLICT OF INTEREST

No conflicts of interest exist regarding the publication of the present study.

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