Is it time to reconsider indications for post-mastectomy chest wall irradiation?

Sir,

These days most of the work in early stage breast cancer is focused on improving methods to predict the chances of recurrence in an individual patient and also on ways to decrease this recurrence, both locoregional and systemic, by incorporating a strategy of individualized, risk based treatment approach. However, there is still a long way to go, as with the currently available adjuvant chemotherapy, radiotherapy, hormonal therapy and molecular therapy the 10 year relapse free survival rates in early stage breast cancer range from 50% to 80%, across various studies and across various risk groups. Indications for these adjuvant therapies, drugs used along with their dosage and duration and techniques employed in radiation continue to be re-defined as newer and newer data comes up.

Here, we will be discussing on two probable indications of post-mastectomy chest wall irradiation in early stage breast cancer, which are currently not the standard of care but have enough evidence of their usefulness to become the standard of care in coming time. First is T1-T2 disease with 1-3 lymph nodes involvement and second is triple negative breast cancer (TNBC) T1-T2 disease with no lymph nodes involved. We have close to 80 years of experience with post-mastectomy chest wall irradiation.\(^{(1,2)}\) These so called older studies have become less relevant in today’s world because they were carried out in an era when adjuvant chemotherapy was not well-defined and also these studies employed older techniques of radiation with variable doses. None of these studies showed overall survival (OS) benefit, some showed disease free survival (DFS) advantage but all of them showed a decrease in the rate of loco regional recurrence. With the advent of well-defined adjuvant chemotherapy and hormonal therapy the role of post-mastectomy chest wall irradiation is redefined. The Danish Breast Cancer Cooperative Group (DBCG) 82b trial showed that at 10 year follow-up, incorporating post-mastectomy chest wall irradiation in high-risk premenopausal patients, i.e., those with T3-T4 tumors or lymph node positive disease resulted in 14% and 9% improvement in DFS and OS, respectively.\(^{(3)}\) The same group in the DBCG 82c trial in post-menopausal high-risk breast cancer patients demonstrated that post-mastectomy chest wall irradiation resulted in 12% and 9% improvement in DFS and OS, respectively at 10 year follow-up.\(^{(4)}\) Because of these studies post-mastectomy chest wall irradiation became a standard of care in high-risk patients, i.e., T3-T4 or \(N \geq 2\) in 2001.\(^{(5)}\) Similar advantage of post-mastectomy
Letters to Editor

and OS. After a median follow-up of 86.5 months, versus ≥4 lymph nodes. irradiation extended to all lymph node positive patients benefit of radiation observed could be due to suboptimal and 11 in British Columbia trial. It was argued that the axillary lymph nodes resected, median of 7 in Danish trials one drawback cited in these studies in the low number of the number of axillary lymph nodes involved. However, one drawback cited in these studies in the low number of axillary lymph nodes resected, median of 7 in Danish trials and 11 in British Columbia trial. It was argued that the benefit of radiation observed could be due to suboptimal lymph node dissection. To address this criticism, another sub-group analysis from the Danish trials considered the subset of 1,152 node-positive patients with eight or more nodes removed (i.e., >median).[7] The overall 15-year survival rate was increased by 9% in patients with either one to three positive nodes or four or more positive nodes. Although the patients with four or more positive nodes had a far greater improvement in local control with RT than did the group with one to three nodes, the survival benefits were similar in both groups.

Another area where role of post-mastectomy chest wall irradiation is being redefined is early stage, node negative TNBC. TNBC patients accounts for about 15% of all types of breast cancers, with a relatively poor outcome after treatment.[8] They are not candidates for adjuvant hormonal and molecular therapy. The only adjuvant therapy recommended in T1-T2, N0 TNBC is chemotherapy. Despite this the recurrence rates in TNBC are high and survival rates poor.[9] Radiotherapy as an adjuvant modality in early stage TNBC has been explored for any benefit in survival outcomes. In a study of 681 patients with stage I-II TNBC addition of radiotherapy after adjuvant chemotherapy has resulted in significant improvement in recurrence free survival (RFS) and OS.[10] After a median follow-up of 86.5 months, 5-year RFS rates were 88.3% and 74.6% for adjuvant chemotherapy plus radiation and adjuvant chemotherapy alone, respectively. Five-year OS were 90.4% and 78.7% for adjuvant chemotherapy plus radiation and adjuvant chemotherapy alone, respectively. The benefit shown is comparable to the benefit of trastuzumab in Human epidermal growth factor receptor-2 (HER-2) positive cases as per the recent 10 year final joint analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials presented at 2012 San Antonio Breast Cancer Symposium. This benefit is also in concordance with another study demonstrating the superiority of breast conserving surgery and radiotherapy over mastectomy in terms of loco-regional RFS.[11] Analysis carried out by DBCG on the patients enrolled in DBCG 82b and 82c trials to find out the impact of estrogen receptor (ER), progesterone receptor (PR) and HER-2 status on the benefits derived from post-mastectomy chest wall irradiation in high-risk patients showed that patients with TNBC had relatively low DFS benefit compared to hormone receptor positive patients and no OS advantage.[12] From these studies we conclude that in TNBC patients addition of post-mastectomy chest wall irradiation is more effective (in terms of RFS and OS) in T1-T2, N0 disease as compared to high-risk T3-T4, node positive disease. This stands in contradiction to our current practice of using irradiation in high-risk TNBC and not using the same in early stage, node negative disease. One possible explanation of this paradox is that node positive TNBC is already a systemic disease at outset considering the aggressive biology of the disease, not amenable to control by addition of local radiation. Node negative TNBC is more likely to be a localized disease, which can be better controlled by local radiation.

Thus, we believe that post-mastectomy chest wall irradiation has a role in T1-2, N1 disease irrespective of ER, PR and HER-2 status and also in T1-2, N0 TNBC. It should be strongly considered in these two settings.

Alok Gupta

Department of Medical Oncology, TMH, Parel, Mumbai, Maharashtra, India.
E-mail: alok Gupta16@yahoo.co.in

REFERENCES

Celiac disease presented after autologous bone marrow transplantation for acute myelogenous leukemia

Sir,

Celiac disease or gluten-sensitive enteropathy is defined as a small intestine disorder which leads to mucosal inflammation and villous atrophy after exposure to dietary gluten and causes different features of intestinal malabsorption.[1] Development of celiac disease in cases of acute leukemia after allogeneic bone marrow transplantation (BMT) from Human leukocyte antigen identical siblings who suffered from celiac disease, have been reported in the literature.[2,3]

We report the first case of celiac disease presented after autologous BMT for acute myelogenous leukemia (AML).

A 31-year-old man presented with chronic diarrhea. He had a history of AML (M4) since 2.5 years ago. After induction chemotherapy, he had received cycles of consolidation chemotherapy and then underwent autologous BMT since he had not HLA-identical sibling donor. He was under observation in short intervals at Oncology clinic without any abnormal finding except persistent pancytopenia due to a hypocellular bone marrow in a heavily treated patient and without any evidences of AML relapse. In the recent visit, he complained chronic diarrhea and weight loss. Physical examination was unremarkable except for asthenia. Laboratory findings were included in Table 1.

Total colonoscopy was normal. Upper gastrointestinal endoscopy showed a loss of folds in the second part of duodenum (D2) and biopsy from D2 showed flattening of duodenal mucosa, intraepithelial lymphocytes, lymphoplasmacytic infiltration in lamina propria, and crypt hyperplasia (Marsh class 3). Immunoglobulin A (IgA) anti-tissue transglutaminase antibodies (IgA-tTG) was markedly elevated to more than 300 u/ml. Bone mass densitometry revealed osteopenia [Table 2].

Diagnosis of celiac disease was made and gluten free diet, multivitamins and mineral replacement therapy was started. We present the first case of celiac disease that presented 2.5 years after autologous stem cell transplantation for AML.

There are inconsistent reports regarding celiac disease after BMT in patients with acute leukemia. In one report, correction of celiac disease after allogeneic BMT for acute leukemia was reported[4] while another reports show the occurrence of celiac disease in recipients of allogeneic BMT for AML from HLA-matched sibling donors who had suffered from celiac disease. There was no report in the literature regarding celiac disease and autologous BMT. We thereby report the first case of celiac disease presented with chronic diarrhea 2.5 years after autologous BMT for AML. If our presented case had a latent celiac disease that presented 2.5 years after autologous BMT or changes in immune function lead to the occurrence of celiac disease are our unanswered questions.