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^{90}Y-ibritumomab tiuxetan, fludarabine, busulfan and antithymocyte globulin reduced-intensity allogeneic transplant conditioning for patients with advanced and high-risk B-cell lymphomas

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Background: Patients with advanced B-cell non-Hodgkin's lymphoma (NHL) refractory to initial chemotherapy or relapsing after autologous stem-cell transplantation have a poor prognosis. Allogeneic stem-cell transplantation after reduced-intensity conditioning (RIC) regimen can be a therapeutic option. However, the high incidence of relapse remains a challenging issue. We speculated that the incorporation of ^{90}Y-Ibritumomab tiuxetan into a fludarabine-based RIC regimen would improve the lymphoma control without overwhelming toxicity. Our aim was to evaluate the safety of ^{90}Y-Ibritumomab tiuxetan in association with such a regimen in a prospective multicenter phase II trial.

Patients and methods: Thirty-one patients with advanced lymphoma from five distinct institutions were included between February 2008 and October 2010. Thirty patients in complete or partial response after failure of a median of 3 (range, 2–4) previous chemotherapy regimens including autologous transplant in 29 were evaluable for nonrelapse mortality (NRM) at day 100 post-transplant that was the primary end point.

Results: With a median follow-up of 32 months (range, 29–60 months), the 2-year event-free and overall survivals of the whole study group were both 80% [95 confidence interval (CI) 60.8% to 90.5%). The 100-day and 2-year post-transplant cumulative incidences of NRM were 3.3% (95% CI 0.2% to 14.9%) and 13.3% (95% CI 5.4% to 33.2%), respectively. The 2-year cumulative incidence of relapse was 6.7% (95% CI 1.7% to 25.4%). The cumulative incidences of grade II–IV and extensive chronic graft-versus-host disease were 27% and 14%, respectively.

Conclusions: For chemosensitive advanced high-risk B-cell lymphoma, the addition of ^{90}Y-Ibritumomab tiuxetan to a RIC regimen based on fludarabine, busulfan and antithymocyte globulin followed by allogeneic transplant is safe and highly effective.clinicaltrials.gov: NCT00607854.

Key words: aggressive lymphoma, allogeneic stem-cell transplantation, ^{90}Y-ibritumomab tiuxetan

introduction

Prognosis of B-cell Non-Hodgkin's lymphomas (NHL) refractory to immunochemotherapy and autologous stem-cell transplant (ASCT) remains poor [1, 2]. In view of evidence suggesting a graft-versus-lymphoma (GVL) effect of transplant [3] the goal of optimizing the benefits of allogeneic stem-cell transplant (allo-SCT) while minimizing toxicity remains at the forefront of clinical research. Promising results in studies using radioimmunotherapy (RIT) suggest it may have a role in pre-transplant conditioning. The reduced-intensity conditioning (RIC) regimens consistently associated with decreased early nonrelapse mortality (NRM) may be particularly useful in heavily pretreated patients at high risk for toxicity [4, 5]. One possible approach to improve outcome may be to reinforce the antilymphoma effect of the

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conditioning regimen without increasing the toxicity. RIT that combines monoclonal antibody targeting and therapeutic doses of radiotherapy is a suitable option. Among the radiolabelled immunoconjugates currently approved for the treatment of B-cell NHL, ^{90}Y-Ibritumomab tiuxetan (Zevalin®, Bayer Health Care then Spectrum Pharmaceuticals, Inc., since November 2012) has substantial activity in lymphoma [6–8] and promising results have been reported when given in combination with high-dose chemotherapy followed by ASCT [9, 10].

Taking into account these data and those of early reports [11, 12], we undertook a multicenter phase II trial in patients with advanced B-cell NHL in order to investigate the hypothesis that the addition of ^{90}Y-Ibritumomab tiuxetan to a fludarabine-based RIC regimen [13] before allo-SCT could safely provide better control of the disease in the immediate post-transplant period allowing for the development of a potent GVL effect and improved outcomes.

patients and methods

patient and donor selection

Inclusion criteria were: age between 18 and 65 years, advanced CD 20+ B-cell lymphoma and complete (CR) or partial response (PR) to the last salvage chemotherapy regimen according to Cheson criteria [14]. Advanced lymphomas were defined as either diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) or low-grade lymphoma in transformation or relapsing after at least two chemotherapy regimens with or without ASCT. Other inclusion criteria were ECOG performance status ≤2, no major organ dysfunction (defined as creatinine clearance <30 ml/min, liver function abnormalities with bilirubin and/or transaminases more than twice the normal upper limit, abnormal cardiac or pulmonary function defined by a left ventricular ejection fraction <50%, or diffusing capacity for carbon monoxide <50%, respectively) and the availability of a related or unrelated donor. Donors fully matched or displaying a single allele disparity for HLA-C or DQB1 were selected on the basis of high-resolution molecular typing for HLA-A, -B, -C, -DRB1 and –DQB1. Donor's G-colony-stimulating factor-mobilized peripheral blood stem cells were recommended for all patients.

Exclusion criteria were: prior allo-SCT, stable or progressive disease according to Cheson criteria, active hepatitis C or HIV infection, other malignancy, pregnancy and breast feeding.

treatment plan and conditioning regimen

The choice of salvage chemotherapy regimen was left to the discretion of the treating physician. A platinum-based chemotherapy regimen with rituximab was used in most cases. Patients were evaluated for response by CT scan according to the Cheson criteria reported in 1999 [14]. The conditioning regimen was started 21 days before allo-SCT and consisted of Rituximab 250 mg/m^2 on days −21 and −14, a single dose of ^{90}Y-Ibritumomab tiuxetan on day −14 at 0.4 mCi/kg with a maximum dose of 32 mCi, followed by fludarabine 30 mg/m^2 daily on days −6, −5, −4, −3 and −2, i.v. busulfan 3.2 mg/kg/day on days −5 and −4 and rabbit antithymocyte globulin (ATG) (Thymoglobulin®, Genzyme) 2.5 mg/kg i.v. on day −1.

Graft-versus-host disease (GVHD) prophylaxis consisted of ciclosporin alone (for patients with 10/10 HLA matched related donor or unrelated donor transplants) or in association with Methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3 and +6) for unrelated donor displaying an HLA mismatch with the recipient. Ciclosporin was continued until day 90 then tapered off by day 180 depending on chimerism and/or GVHD occurrence. Donor lymphocyte infusion (DLI) was allowed for incomplete response and mixed chimerism. Patients were restaged with CT scans at 1, 3, 6, 12 and 24 months after transplantation. GVHD was assessed 1, 3, 6, 9 and 12 months after transplant and donor chimerism evaluation was evaluated 1 and 3 months after transplant.

Toxicities were grade according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.

end points

The primary objective of the study was to evaluate the safety of ^{90}Y-Ibritumomab tiuxetan as part of a fludarabine-based RIC regimen defined by NRM by day 100. NRM was defined as death from any cause except disease progression. All deaths were reviewed by an independent committee. Secondary end points included overall PR and CR rates, event-free survival (EFS) and overall survival rates, 2-year cumulative incidence of relapse, hematologic recovery at day 30 (defined as absolute neutrophil count >500/μl and platelets >20 000/μl for 3 consecutive days), incidences of grade II–IV acute GVHD, chronic GVHD and donor chimerism.

statistical analysis

The study was designed to reject the hypothesis of a 100-day NRM ≥20% in a single-arm phase II trial [15]. Sample size calculation was based on the hypothesis that the treatment would be considered excessively toxic if d-100 NRM was ≥20% and then should be rejected with a 5% type 1 error rate, and to assure that the treatment would be considered safe if NRM were ≤5% with 80% power. The calculated sample size was 30 patients, and the therapeutic protocol would be considered too toxic if ≥3 patients died from a transplant related cause within 100 days.

EFS time was measured from transplant to progression or death from any cause. Overall survival (OS) time was measured from transplant to death from any cause. Survival curves and rates were estimated using the non-parametric Kaplan–Meier method. Cumulative incidence probabilities of nonrelapse (or relapse) mortality considering relapse (or nonrelapse) mortality as a competing risk were used to draw and estimate nonrelapse (or relapse) mortality probability [16]. Because of small sample size, study of prognostic factors on OS was based on univariate analysis. The following prognostic factors were considered: response according to Cheson criteria, histologic subtypes, related or unrelated donor, age at transplant, time between auto and allo-SCT and between diagnosis and allo-SCT, number of prior regimens and number of infused CD34+ cells. Cox regression models were used and hypotheses (risk proportionality and linearity of the association for quantitative factors) were systematically checked. A P value of ≤0.05 was considered statistically significant.

Acute and chronic GVH times were defined as the time from transplant to GVHD. GVHD time was censored at the date of death or at the date of day 90–100 visit for acute or at one year visit for chronic GVHD. Cumulative incidences were estimated with death as a competing risk.

Statistical analyses were carried out by the statistician of the clinical trial unit using SAS software (SAS Institute, v9.1.3, Cary, NC).

The protocol was conducted in accordance with Good Clinical Practice rules and all patients gave written informed consent to participate in the study before beginning the conditioning regimen. It was approved by the local ethics committee and the national regulatory authority (Agence Nationale de Sécurité des Médicaments et des produits de santé, ANSM) and registered under ClinicalTrials.gov NCT 00607854.

results

patient and donor characteristics

Thirty-one patients were included in five centers between February 2008 and October 2010. One patient had evidence of progressive disease immediately after receiving ^{90}Y-Ibritumomab tiuxetan and

before the RIC regimen and was withdrawn from the study. The 30 remaining patients received the planned treatment and are evaluable for the primary and secondary end points. The characteristics of the patients are summarized in Table 1. Among the 10 patients with low-grade lymphoma, 5 had had histological transformation to high-grade lymphoma and 9 patients had relapsed after second-line ASCT. All patients had received rituximab in their prior chemotherapy regimens.

disease response and survival

All patients were assessable for response and survival. With a median follow-up of 32 months (range, 29–60), the 2-year EFS was 80% [95 confidence interval (CI) 60.8% to 90.5%] (Figure 1) and the 2-year OS was 80% (95 CI 60.8% to 90.5%) (supplementary Figure S1, available at *Annals of Oncology* online). The 2-year EFS and OS for DLBCL, MCL and low-grade lymphoma were both 78.6% (95% CI 47.2% to 92.5%), 83.3% (95% CI 27.3% to 97.5%) and 80% (95% CI 40.9% to 94.6%), respectively (Supplementary Figures S3 and S4, available at *Annals of Oncology* online).

Seventeen patients were in CR at transplant (DLBCL = 10, MCL = 5, low-grade lymphoma = 2). Two of these patients (DLBCL = 1, MCL = 1) died of NRM (GVHD) and 15 patients were still alive in CR at last follow-up (October 2012). Of 13 patients in PR at transplant (DLBCL = 4, MCL = 1, LGL = 8), 2 died of NRM (GVHD = 1, suicide = 1) and 2 of progressive disease. Nine patients (DLBCL = 2, MCL = 1, LGL = 6) were still alive in CR at last follow-up. Among these 13 patients, 11 (DLBCL = 2, MCL = 1, LGL = 8) converted to CR after allo-SCT.

No prognostic factor for survival was identified (Supplementary Table S1, available at *Annals of Oncology* online). However, there was a trend for better survival for patients transplanted in CR (HR, 0.38; 95% CI 0.07–2.05) or with a number of infused CD34+ cells >6.5 × 10^6/kg (HR, 0.19; 95% CI 0.02–1.59).

Table 1. Patient characteristics

N = 30	Value
Age (years), median (range)	57 (32–64)
Male/female, no. (%)	22/8 (73.3/26.7)
Histology, no. (%)	
DLBCL	14 (46.7)
MCL	6 (20
LGL	10 (33.3)
Prior regimens, median (range)	3 (2–4)
Prior ASCT, no. (%)	29 (96.7)
Interval (months), median (range)	
Diagnosis, allo-SCT	37 (8–108)
ASCT, allo-SCT	18 (2–56)
CR/PR (before allo-SCT), no. (%)	17/13 (56.7/43.3)
Donor, no. (%)	
Matched-related	20 (66.7)
Matched-unrelated	8 (26.7)
mm C/DQB1	1/1 (3.3/3.3)
Stem cell origin, no. (%)	
PBSC	30 (100.0)
Median number of infused CD34+ cells (range)	6.5 × 106/kg (1.7–16.9)
GVH prophylaxis, no. (%)	
CsA	29 (96.7)
CsA + Mtx	1 (3.3)

CR, complete response; PR, partial response; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; LGL, low-grade lymphoma; ASCT, autologous stem-cell transplantation; allo-SCT, allogeneic stem cell transplantation; mm, mismatch for HLA-C or DQB1; PBSC, peripheral blood stem cells; CsA, ciclosporin, Mtx, methotrexate.

toxicity and graft-versus-host disease

There was no unanticipated hematologic toxicity. All patients had grade 4 neutropenia and 22 patients (73%) grade 4 thrombocytopenia. The median time to reach absolute neutrophils >500/μl and platelets >20 000/μl were 17 days (range, 12–22) and 11 days (range, 6–16). By day 30, all patients experienced a sustained engraftment without secondary graft failure. At day 90, chimerism was assessed on peripheral T cells in 18 and total nucleated cells in 14 patients (of 28 patients alive). In 15 cases (83.3%), there was conversion to full peripheral T-cell- and, in 12 patients (85.6%), to total nucleated cells donor chimerism, respectively. One patient with mixed chimerism received a DLI early after transplant. He died at day 41 from NRM.

The most common extra-hematologic toxicity was infection (1 grade 4 and 10 grade 3). Seventeen patients (57%) had at least one episode of infection from bacterial ($n = 11$), viral ($n = 9$), fungal ($n = 5$) or parasitic ($n = 1$) origin. There was no significant mucositis and no significant toxicities in other organs.

Sixteen patients experienced grade I–IV acute GVHD. The target lesions of aGVHD were skin (14 patients, 2 with grade III/IV), liver (4 patients, 2 with grade III/IV) and the gastrointestinal tract (7 patients, 1 with grade III/IV). The cumulative incidence of grade II–IV aGVHD was 26.7% ($n = 8$; grade II: 4 patients, grade III: 3 patients, grade IV: 1 patient). Chronic GVHD occurred in 12 of 29 patients alive at day 100 (CI 42.9%; 95% CI 27.9% to 65.7%) and was extensive in 4 (cumulative incidence = 14.3%).

nonrelapse mortality and relapse

Six patients died. Among them, four patients died from NRM (aGVHD = 3, suicide = 1) on days 41, 118, 323 and 481 after transplant and two patients died from progression on days 64 and 115. The cumulative incidences of NRM at day 100 and at 2 years were 3.3% (90% CI 0.2% to 14.9%) and 13.3% (95% CI 5.4% to 33.2%), respectively (Figure 2). No other relapses were detected on re-staging at 2 years with a 2-year cumulative incidence of relapse mortality of 6.7% (95% CI 1.7% to 25.4%) (Supplementary Figure S2, available at *Annals of Oncology* online).

discussion

In the present multicenter trial, we can consider that the addition of ^{90}Y-ibritumomab tiuxetan to a RIC regimen before allo-SCT from HLA matched related or unrelated donors was feasible and safe with a 2-year NRM of 13%. We show that this regimen combining ^{90}Y-ibritumomab tiuxetan with fludarabine, busulfan and antithymocyte globulin induced CR in 11 of 13

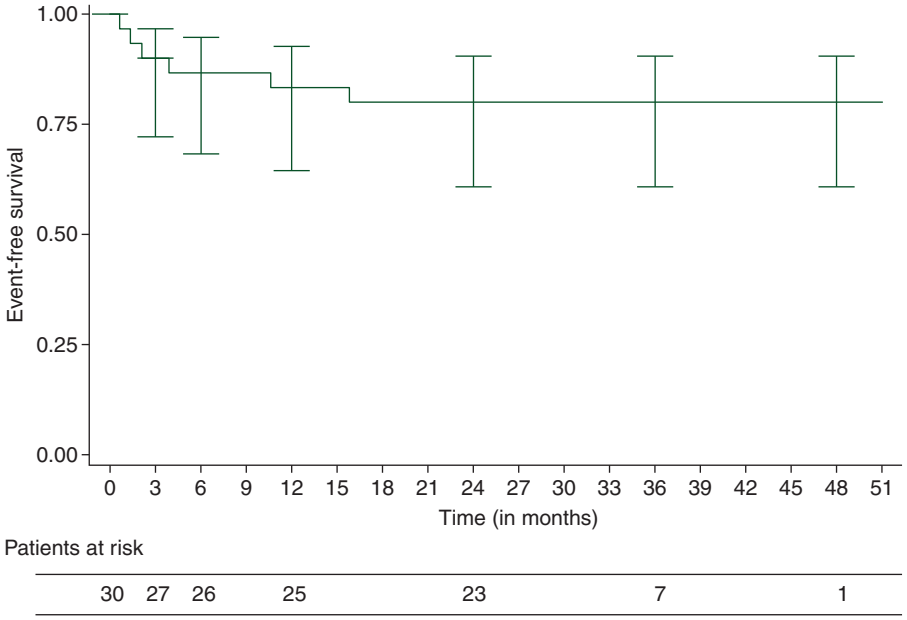

Figure 1. Event-free survival.

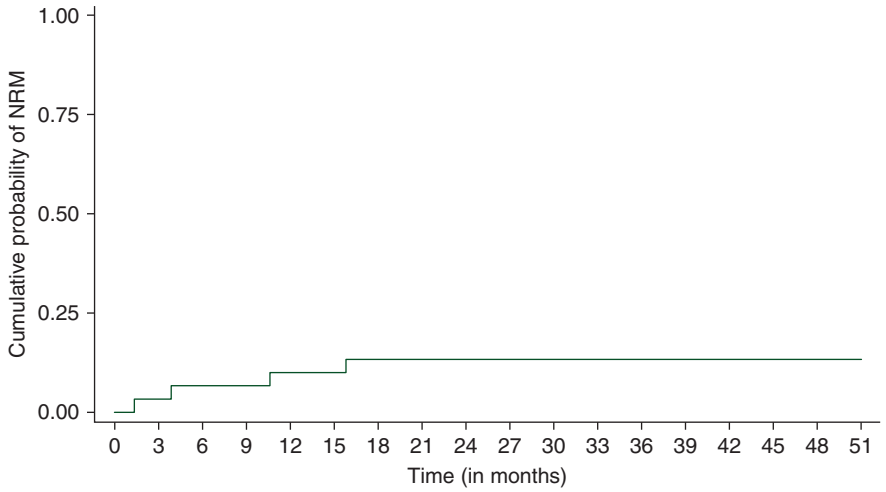

Figure 2. Cumulative risk of NRM at 2 years.

patients who had PR at time of transplant and that, with a minimum follow-up of 2 years after transplant, no patient relapsed beyond 3 months after transplant. Altogether, low NRM and highly efficient disease control led to OS and PFS of 80% at 2 years with a plateau beyond 15 months. Several points may be put forward to explain these results:

First, despite the fact that patients had advanced diseases having failed a median of three lines of previous immunochemotherapy, including high-dose therapy with ASCT, their diseases remained sensitive to the last regimen. Clearly, selecting responding patients is essential to reduce NRM [17–19] and improve survival. It is also important to note that since no PET-CT was done, patients with morphologic PR could have been in CR. Additionally, the median number of previous regimens was low (3) compared with previous studies.

Second, the low incidence of acute grade II–IV (27%) and extensive chronic GVHD (14%) may also have contributed to the low NRM. This was clearly the case in two studies that combined RIT with RIC before allo-SCT in patients with advanced NHL [20, 21]. In these trials, rates of acute GVHD were 43% and 67% and 2-year incidences of NRM were 42% and 45%. Early taper of immunosuppression, advanced disease and absence of *in vivo* T-cell depletion could partly explain these high incidences. We can hypothesize that the use of ATG may have contributed to the low incidence of GVHD we observed [13]. We can also speculate that the depletion of potential antigen presenting B cells by CD20-targeted RIT could have completed the beneficial donor T-cell depleting effect of ATG [22].

The 2-year incidence of relapse of 7% in our study is lower than usually reported in similar patients [19, 23]. These results might not only be due to the selection of patients with responding disease, but also to the addition of ^{90}Y-ibritumomab tiuxetan to the RIC regimen since targeting B tumor cells may have decreased the residual disease as evidenced by the conversion of PR to CR in our study and in Gopal's trial [24]. We can hypothesize that this very low tumor burden allowed for a GVL

effect hence inducing a potent disease control with a prolonged PFS (2-year PFS: 80%). However, it is noteworthy that when Alemtuzumab was used as GVHD prophylaxis in an RIT-containing RIC regimen, incidences of relapses of 50% were reported [25]. The low ATG dose we used (2.5 mg/kg) might have allowed allogeneic lymphoid cells to exert a GVL effect without severe GVHD. Such a low dose of ATG, however, is thought not to adequately curb GVHD [13] but this may not be the case when combined with *in vivo* B-cell depletion permitted by anti-CD20 targeted therapy as discussed earlier. The main studies with RIT and allo-SCT are summarized in supplementary Table S2, available at *Annals of Oncology* online.

Although limited, the number of patients included in our trial was sufficient to demonstrate the excellent tolerance of this ^{90}Y-ibritumomab tiuxetan containing RIC regimen. It also showed excellent efficacy in advanced but still chemosensitive high-risk B-cell lymphomas. Our study showed a trend for better survival in patients in CR at time of transplant. This is in line with the demonstrated need for obtaining the best disease control before transplant to achieve prolonged disease-free survival.

Finally, these encouraging results prompted us to initiate a phase III prospective, randomized and multicenter trial in patients with advanced but therapy-sensitive B-cell NHL to better define the potential benefit effect of RIT on disease control and/or GVHD prevention after allogeneic transplant.

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disclosure

The authors have declared no conflicts of interest.

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Comparison of outcomes of locoregionally advanced oropharyngeal and non-oropharyngeal squamous cell carcinoma over two decades

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Background: Human papillomavirus (HPV) has emerged as a causative agent and positive prognostic factor for oropharyngeal (OP) head and neck squamous cell cancer (HNSCC). This prompts inquiry into whether therapy improvements or increasing incidence of HPV drives the apparent improvements in HNSCC outcomes observed in non-randomized clinical trials.

Patients and methods: We reviewed all locoregionally advanced HNSCC patients treated with chemotherapy and radiation in prospective institutional trials at a single institution. Patients were divided into three groups (1, 2, 3) according to treatment time period (1993–1998, 1999–2003, 2004–2010, respectively). We reasoned that if a favorable trend was observed over time in OP but not non-OP patients, HPV status may be confounding treatment effects, whereas this would be unlikely if both subgroups improved over time.

Results: Four hundred and twenty-two patients were identified with OP (55.7%) and non-OP (44.3%) HNSCC. Five-year OP overall survival (OS) improved from 42.3% (group 1) to 72.5% (group 2), and 78.4% (group 3), adjusted $P = 0.0084$. Non-OP 5-year OS was 51.0% (group 1), 58.8% (group 2), and 66.3% (group 3), adjusted $P = 0.51$. Five-year recurrence-free survival (RFS) improved for OP groups from 42.3% to 68.4% to 75.8% (adjusted $P = 0.017$). Non-OP 5-year RFS was 42.9%, 53.6%, and 61.7% for sequential groups (adjusted $P = 0.30$). Five-year OP distant failure-free survival (DFFS) improved from 42.3% to 71.1% to 77.8% (adjusted $P = 0.011$). Five-year non-OP DFFS was 46.9%, 57.1%, and 66.0% for sequential groups (adjusted $P = 0.38$).

Conclusions: Over the past two decades, OP HNSCC outcomes improved significantly, while non-OP outcomes only trended toward improvement. Although our patients are not stratified by HPV status, improving OP outcomes are likely at least partly due to the increasing HPV incidence. These data further justify trial stratification by HPV status, investigations of novel approaches for carcinogen-related HNSCC, and current de-intensification for HPV-related HNSCC.

Key words: HPV, head and neck, squamous cell carcinoma, oropharyngeal

introduction

Treatment of locoregionally advanced head and neck squamous cell carcinoma (HNSCC) requires multimodality therapy, including definitive chemoradiation therapy (CRT) or surgery with adjuvant therapy for high-risk pathologic features. Definitive CRT has gained popularity due to increasing prioritization of organ preservation with multiple series demonstrating favorable outcomes [1–3]. CRT with concurrent cisplatin is the standard of care for the treatment of locoregionally advanced disease [4]. Our institutional experience with hyperfractionated CRT and combination chemotherapy has demonstrated promising clinical outcomes in serial trials [5–12].

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