Safety of concomitant delivery of radiotherapy for second primary malignancy in patients with chronic lymphocytic leukemia treated with continuous novel agents

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BACKGROUND

- Patients with chronic lymphocytic leukemia (CLL) are at elevated risk of developing non-hematologic malignancies.
- Radiation therapy (RT) is a critical component of management in localized solid organ malignancies.
- CLL patients treated with novel agents (e.g., BTKi, venetoclax) receive continuous daily dosing and unnecessary dose interruptions are avoided.
- Safety data are lacking to guide the concurrent administration of radiation therapy for a second cancer in patients receiving ongoing CLL novel agent treatment.

METHODS

- We identified patients treated concurrently with novel agents for CLL and RT for second primary malignancy at Mayo Clinic from 2014-2022.
- Adverse events within 3 months of RT were evaluated using the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematological toxicity and the Common Terminology Criteria for Adverse Events (CTCAE) version 5 for non-hematological toxicity.
- Patients without seamless, concurrent treatment with novel agent therapy and RT were excluded; sequential therapy was not considered. The Wilcoxon signed-rank test was used to assess the median difference before and after radiation.

Novel Agent	N=26
Ibrutinib	23 (88.5%)
140 mg daily	6 (23.1%)
140 mg every 3 days	1 (3.8%)
280 mg daily	6 (23.1%)
420 mg daily	10 (38.5%)
Venetoclax	1 (3.8%)
200 mg daily	
Acalabrutinib	2 (7.7%)
100 mg twice daily	1 (3.8%)
100 mg daily	1 (3.8%)

Prior Therapies	
Number of CLL therapies prior to NA	
0	6 (23.1%)
1	9 (34.6%)
2	6 (23.1%)
3	3 (11.5%)
4	2 (7.7%)
Number of CLL therapies prior to NA	
Mean (SD)	1.5 (1.2)
Median	1
Range	(0.0-4.0)

Secondary Malignancy	
adenocarcinoma prostate	9 (34.6%)
head/neck carcinoma	8 (30.8%)
NSCLC	3 (11.5%)
glioblastoma	1 (3.8%)
IDC breast	1 (3.8%)
plasmacytoma	1 (3.8%)
melanoma	1 (3.8%)
RCC	1 (3.8%)
thymoma	1 (3.8%)

Radiation	
Radiation Type	
Photon	18 (69.2%)
Proton	7 (26.9%)
Both	1 (3.8%)
Radiation Sensitizing Agent	
Yes	2 (7.7%)
No	24 (92.3%)
Radiation Location	
pelvis	8 (30.8%)
head/neck	8 (30.8%)
Lung	4 (15.4%)
brain	1 (3.8%)
chest wall	2 (7.7%)
mediastinum	1 (3.8%)
pelvis+lung	1 (3.8%)
renal	1 (3.8%)
Radiation Intent	
Palliative	1 (3.8%)
Neoadjuvant	0
Adjuvant	10 (38.5%)
Definitive	15 (57.7%)

Table 1.

Hematological adverse events

	Pre Radiation	Post Radiation	P value	CTCAE Criteria	Attribution	iwCLL Criteria
Hemoglobin, median (range) g/dL	13.3(10.1-18.6)	12.4(5.9-17.4)	0.001	not applicable: 8 (30.8%) grade 1: 13 (50.0%) grade 2: 3 (11.5%) grade 3: 2 (7.7%) grade 4: 0 grade 5: 0	not applicable: 8 (30.8%) unrelated: 8 (30.8%) unlikely: 1 (3.8%) possibly: 7 (26.9%) probably: 2 (7.7%)	grade 0: 17 (65.4 %) grade 1: 6 (23.1%) grade 2: 3 (11.5%) grade 3: 0 grade 4: 0
Platelet Count, median(range) x10^9/L	175.5(78.0-373.0)	140.5(10.0-287.0)	0.004	not applicable: 15 (57.7%) grade 1: 8 (30.8%) grade 2: 1 (3.8%) grade 3: 1 (3.8%) grade 4: 1 (3.8%)	not applicable: 15 (57.7%) unrelated: 3 (11.5%) unlikely: 1 (3.8%) possibly: 5 (19.2%) probably: 2 (7.7%)	grade 0: 19 (73.1%) grade 1: 3 (11.5%) grade 2: 2 (7.7%) grade 3: 0 grade 4: 2 (7.7%)
Neutrophil Count, median(range) x10^9/L	4.4(1.2-19.3)	3.4(0-6.6)	<0.001	not applicable: 21 (80.8%) grade 1: 1 (3.8%) grade 2: 2 (7.7%) grade 3: 1 (3.8%) grade 4: 1 (3.8%)	not applicable: 19 (73.1%) unrelated: 1 (3.8%) unlikely: 0 possibly: 4 (15.4%) probably: 2 (7.7%)	grade 0: 19 (73.1%) grade 1: 5 (19.2%) grade 2: 0 grade 3: 1 (3.8%) grade 4: 1 (3.8%)

Frequency of grade 3 and 4 toxicities per patient

Patient	Novel Agent	Second Primary Malignancy	RT cGy/ fraction	Grade 3/4 Adverse Events*
1	Ibrutinib	head/neck cancer	6000/30 with weekly cisplatin	grade 4 thrombocytopenia grade 4 neutropenia grade 4 febrile neutropenia grade 4 lung infection grade 3 acute kidney injury grade 3 mucositis oral
2	ibrutinib	head/neck cancer	6600/33	grade 4 thrombocytopenia grade 4 acute kidney injury grade 4 sepsis grade 5 respiratory failure
3	ibrutinib	head/neck cancer	6600/33	grade 3 neutropenia

Table 2. *iwCLL used for hematological adverse events

RESULTS

- Average age at start of concurrent radiation treatment 68 years (range: 51-85 years).
- Four patients had del(17p) and 18 patients had unmutated IGHV.
- The most common conventionally fractionated prescriptions (cGy/fx) were 6000/30 (n=6) and >6000-7020/20-33 (n=7). SBRT ranged from 3300/5 to 5400/3 (n=8). Five patients received other, varied RT prescriptions.
- 58% of patients were receiving a reduced dose prior to RT start. There were no reports of dose reduction in anticipation of radiation therapy.

RESULTS CONT.

- Grade ≥3 hematological toxicities occurred 3 patients detailed in Table 2
- Grade ≥3 non-hematological toxicities occurred in 2 patients that required hospitalization for critical illness (Table 2)
- There were no reports of tumor lysis syndrome, malignant hypertension, grade ≥3 hemorrhage or severe cardiac arrhythmias.
- The most common side effects documented were grade 1 fatigue (n=7, 26.9%) and grade 1 radiation dermatitis (n=5, 19.2%).
- Every patient completed their course of radiation and there were no cases of dose reduction for radiation.

CONCLUSIONS

- This study provides the first assessment of patients with CLL on novel agents who were concurrently treated with radiotherapy for a subsequent solid organ malignancy.
- Our study found limited CLL-treatment related adverse events. Radiation side effects did not appear to be heightened.
- Our results suggest that concurrent treatment should be a shared decision-making discussion regarding potential harms versus benefits.
- A comprehensive clinical evaluation that accounts for the patient's medical comorbidities and personal risk factors should inform the discussion.