Radioimmunotherapy combined with antibody–drug conjugate–induced radiosensitization leads to long-term remission in mycosis fungoides

M. Oymanns, K. Elsayad, M. Daum-Marzian, R. Abu-Dawud, M. Motiei, D. R. Steinke, K. A. Brücksken, H. T. Eich, B. Greve, C. Assaf,
Correspondence: mathias.oymanns@helios-gesundheit.de

Background

Patients with tumor-stage mycosis fungoides (MF; ≥IIB) have limited treatment options and poor survival (1–5 years). Brentuximab vedotin (BV), an anti-CD30 antibody–drug conjugate, is effective in CD30+ CTCL but limited by delayed responses and peripheral neuropathy.[1] Radiotherapy, especially low-dose total skin electron beam therapy (TSEBT; e.g. 8 Gy/2 fractions), remains standard in MF.[2] Preclinical data indicate synergy between BV and radiotherapy via radiosensitization and immune modulation.[3]

Patients and Findings

We retrospectively analyzed 14 patients with stage IIB MF treated with concurrent BV and ultra-hypofractionated low-dose TSEBT (2 × 4 Gy) (Fig. 1). All had CD30+ lesions (median 5%) and a median of 3 prior systemic therapies. BV (1.8 mg/kg) started on day 1 of TSEBT (median 9 cycles). Eleven patients (79%) received maintenance therapy (mainly methotrexate).

Median age was 62; 8 had folliculotropic MF; no large cell transformation (i.e. >25% of large lymphocytes within the infiltrates). Baseline mSWAT 49 (IQR 41–72) improved to 3 (0–18) at 3 months (p=0.005).
Clinical responses: 9 CR (64%), 2 VGPR, 3 PR → ORR 100%.
Median time to response: 12 days. After 12 months' follow-up, no tumor-stage recurrences; median PFS and TTNT not reached (Fig. 2a).

Side effects

Treatment was well tolerated: 4 patients (29%) had mild rash, 2 (14%) grade 1–2 neuropathy, no grade ≥3 events. Compared to ALCANZA (median response 83 days; neuropathy 67%)[1], responses were faster (12 days) and toxicity lower. A prior case series (n=3) suggested benefit[4]; our data confirm safety and high efficacy in a larger cohort.

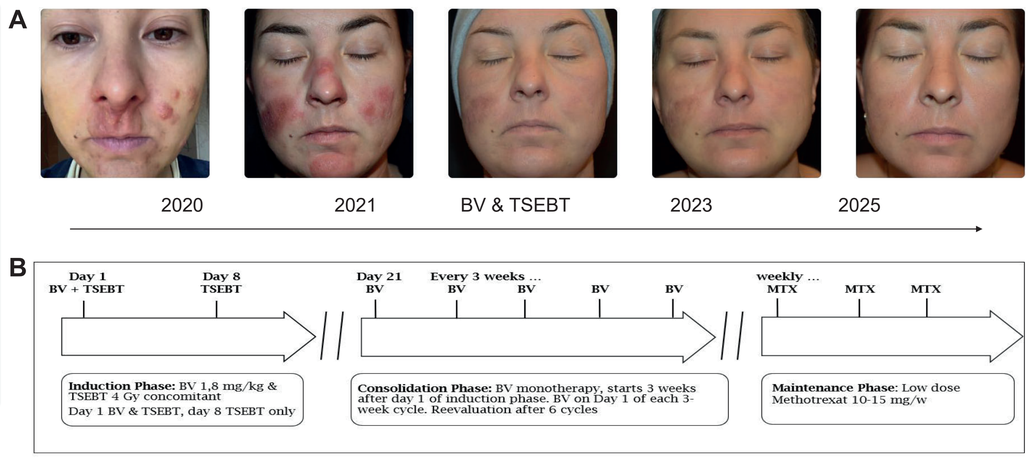

Figure 1: (a) Follow-up of a female patient with tumor stage MF. 2020 & 2021: Prior to concurrent BV and TSEBT. Currently complete remission and maintenance therapy with low-dose Methotrexat for over 3 years. (b) **Treatment Scheme**: Induction and Consolidation Phase followed by Maintenance Phase.

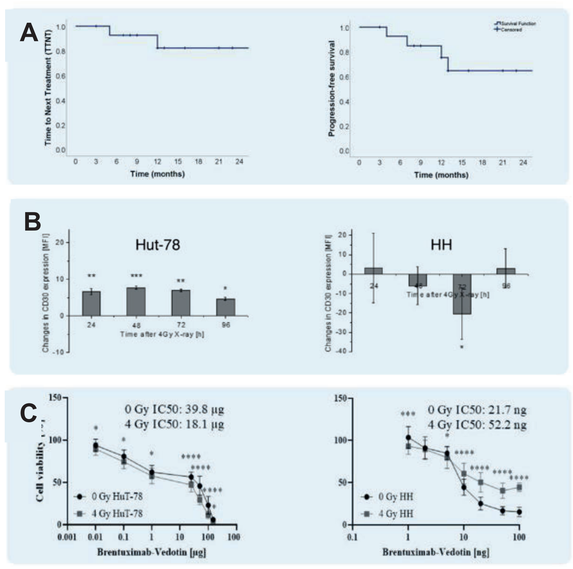

Figure 2: (a) Kaplan-Meier estimates of time to next treatment (TTNT) and progression-free survival (PFS) of the whole cohort (n = 14). (b) HuT-78 cells showed a significant radiation-induced increase in CD30 expression across all time points, while a decrease was measured in HH cells, but only for 72h with significance. (c) Irradiation changed the IC50, while in the HuT-78 cells, the IC50 fell from 39.8 µg/ml to 18.1 µg/ml as a result of irradiation, it increased in the HH cells from an initial 21.7 ng/ml to 52.2 ng/ml after radiation treatment. (n=3, *=0.05, **=0.005, ***=0.0005, ****=0.00005).

Experimental findings

To assess radiation effects, HuT-78 and HH cells were irradiated with 4 Gy and analyzed by flow cytometry. Basal CD30 expression was significantly higher in HH cells. After irradiation CD30 expression increased in HuT-78 cells but decreased in HH cells (Fig. 2b). Correspondingly, BV sensitivity improved in HuT-78 (IC50 39.8 → 18.1 µg/ml) and declined in HH (IC50 21.7 → 52.2 ng/ml) (Fig. 2c). These findings suggest radiation can enhance BV efficacy, particularly in low-CD30–expressing cells, supporting the observed clinical synergy.

Discussion

Multiple mechanisms may explain the improved response. MMAE, the cytotoxic payload of BV, disrupts microtubules and acts as a radiosensitizer by impairing DNA repair.[3] In combination with radiotherapy, this may enhance DNA damage, antigen release, and immunogenic cell death.[5] Preclinical data show MMAE-ADCs improve CD8+ T-cell–mediated tumor control with radiotherapy.[6] Reduced cumulative BV doses may lower toxicity, while maintaining strong efficacy, as observed in our cohort.

Conclusion

This study is limited by its retrospective design and small sample size. Nevertheless, the observed 100% ORR, rapid time to response, and low toxicity support the combination of BV and ultra-hypofractionated TSEBT as a promising therapeutic strategy for advanced MF. Maintenance therapy—here, with methotrexate—may further enhance durability of response.[7,8] Our findings align with emerging evidence that low-dose TSEBT can safely and effectively complement systemic therapies.[2] Prospective clinical trials are warranted to validate this radioimmunotherapy approach and to better characterize patient subsets most likely to benefit.

Research in Context

What is already known about tahis topic?
BV and TSEBT are effective treatments for CTCL. BV is a known radiosensitizier which has been shown in *in vitro* studies from organ derived neoplasia. There is an incomplete understading of the synergistic effects of BV and TSEBT in treatment for CTCL.

What does this study add?
For the first time patients underwent concomitant BV and TSEBT for tumor stage MF with promising results.
For the first time CTCL cell lines have been investigated for the radiosensitizing effects of BV.

What is the translations message?
In patients with advanced CTCL treated with concomitant BV and TSEBT, the therapy demonstrated high efficacy whie reducing toxicities.

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