

“focus on...” session: radioimmunotherapy

015 RADIOIMMUNOTHERAPY FOR INDOLENT NON HODGKIN LYMPHOMA WITH ¹³¹I-RITUXIMAB IN CLINICAL PRACTICE: 8 YEAR SINGLE INSTITUTION EXPERIENCE OF 129 CONSECUTIVE PATIENTS

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Background: Radioimmunotherapy (RIT) with ⁹⁰Y-ibritumomab (Zevalin[®]) and ¹³¹I-tositumomab (Bexxar[®]) in relapsed/refractory indolent lymphoma has ORR 60-83% and CR 15-52%. In clinical practice however, ORR 47% and CR 13% are lower, with grade 3/4 neutropenia in 55% and thrombocytopenia in 56%.

¹³¹I-rituximab in clinical trial gave ORR 76% and CR 53% with grade 4 toxicity, neutropenia 4% and thrombocytopenia 16%. We evaluated our clinical experience in 129 consecutive patients.

Methods: Patients with ANC >1.5/nl and platelets >100/nl received 4 once weekly doses of rituximab 375mg/m² and one individualised ¹³¹I-rituximab therapy activity predicated upon 0.75Gy whole body radiation exposure. Patients were monitored with weekly FBEs until recovery from nadir. Primary response assessment was by CT/PET at 12 weeks.

Results: 129 consecutive RIT patients May 1999 to January 2008 were analysed, sixty five being treated on a phase 2 trial. Median age was 62 years, 70 males and 59 females. Histological subtypes included follicular lymphoma (FL) 92 (73%); grade1 38%, grade 2 33%, grade 3 17% and grade unspecified 8%. Eighteen (14%) patients had SLL, 5 MALT, 5 mantle. Patients had received a median of 3 prior regimens of chemotherapy. Response was evaluable in 119 median follow up 31 months; ORR 68% (80) CR/CRu 50.4% (60) for all patients. Subset analysis showed improved CR/CRu rates in patients <60 vs >60 yrs (60% vs 33%; p= 0.012) and in stage 1/2 vs stage 3/4 (67% vs 37%; p=0.014). The CR/CRu for FLIPI 0/1, 2 and ≥3 was 70%, 47% and 30% respectively (p=0.018). The median PFS was 11 months and CR/CRu 21 months. Haematological toxicity evaluable in 114 patients with grade 4 neutropenia in 14 (12%) and thrombocytopenia in 13 (11%) median time to nadir 6 and 7 weeks respectively. Platelet transfusions were required in 3, G-CSF in 1 and antibiotics in 2 patients. Grade 4 anemia occurred in one patient. 5 developed myelodysplasia.

Conclusion: In house preparation of ¹³¹I-rituximab provides effective, safe, routine treatment for outpatients with relapsed or refractory indolent lymphoma beyond the clinical trial setting with half these patients achieving complete remission

016 OUTCOME OF 87 PREVIOUSLY UNTREATED INDOLENT NON-HODGKIN'S LYMPHOMA PATIENTS TREATED WITH FLUDARABINE AND MITOXANTRONE CHEMOTHERAPY FOLLOWED BY ⁹⁰Y IBRITUMOMAB TIUXETAN

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Introduction: ⁹⁰Y Ibritumomab Tiuxetan (⁹⁰Y-IT) has emerged as an important treatment option for B-NHL.

Material and methods: From June 2004 to April 2006, 15 institutions treated 87 indolent non-Hodgkin's lymphoma (NHL) using a new regimen consisting of 6 cycles of fludarabine and mitoxantrone (FM) chemotherapy followed by ⁹⁰Y-IT. Median age was 56 years (range 30-82). 38 were male and 49 female. 27 patients were stage III, 60 stage IV (53 with bone marrow involvement). According to histology, 61 were follicular lymphoma (FL) grade I-II, and 26 indolent non-FL.

Results: After FM, overall response rate was 92% including 64% (56 patients) complete remission (CR) and 28% (25 patients) partial remission (PR). From the 77 responding patients (56 CR and 21 PR) evaluable for subsequent ⁹⁰Y-IT, 19/21 [90.5%; 12/14 (86%) in FL; 7/7 (100%) in indolent non FL] PR patients obtained CR at the end of the treatment. Finally, after fludarabine and mitoxantrone plus ⁹⁰Y-IT 75/77 (97%) patients obtained CR. With a median follow-up of 33 months (range, 24-51 months), 15 (10 FL and 5 indolent non FL) patients showed relapse; the estimated 3-year progression-free survival is 80%, with a 3-year overall survival of 100%. The ⁹⁰Y-IT toxicity included grade 3 hematologic toxicity in 52/77 patients; 26 (34%) patients received transfusions.

Conclusions: This study has established the feasibility, tolerability, and efficacy of chemotherapy + radioimmunotherapy for untreated indolent NHL.

017 YTTRIUM-90 IBRITUMOMAB TIUXETAN (⁹⁰Y-ZEVALIN) COMBINED WITH THE NOVEL EXPANDED PORPHYRIN MOTEXAFIN GADOLINIUM (MGD, XCYTRIN) PRODUCES RAPID AND SUSTAINED COMPLETE REMISSIONS (CR) IN PATIENTS WITH RITUXIMAB-REFRACTORY FOLLICULAR LYMPHOMA: FINAL RESULTS OF A PHASE I/II CLINICAL TRIAL

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Introduction: MGd is a novel anti-cancer agent that induces caspase-dependent apoptosis in lymphoma by targeting oxidative stress proteins and has been shown to enhance ionizing radiation. We conducted a phase I/II clinical trial for patients (pts) with relapsed/refractory lymphoma using fixed-dose ⁹⁰Y-Zevalin combined with increasing doses of MGd (2.5-5.0 mg/kg).

Methods: Pts received daily MGd on days 1-4 (¹¹¹Indium-Zevalin day 1) and days 8-11 (⁹⁰Y-Zevalin day 8). Response was assessed by International Workshop criteria (Cheson, 1999), with initial CTs performed 4 weeks after ⁹⁰Y-Zevalin. 30 pts enrolled; 28 are evaluable.

Results: 32% of all pts were > age 75 years (Table). 82% of all pts were rituximab-refractory (Rit-Ref) defined as no response or time to progression (TTP) <6 months (mon). 4 pts received 0.3 mCi/kg ⁹⁰Y-Zevalin, while the remainder (n=24) received 0.4 mCi/kg. No dose limiting toxicity was seen. No grade 4 non-hematologic toxicities were seen. Hematologic toxicities included: 29% grade 3/4 neutropenia (7% grade 4), 46% grade 3/4 thrombocytopenia (0% grade 4), and 18% grade 3/4 anemia (0% grade 4). Overall response rates (ORR), CR, and overall survival (OS) rates are shown (Table).

	All Pts (n=28)	Ritux-Refac FL (n=14)
Median age, years (range)	65 (47-87)	60 (47-85)
ORR (CR) at 4 weeks	57% (21%)	86% (21%)
Median prior treatment (range)	3 (1-5)	3 (1-4)
Bulky (>5cm)	54%	64%
Best ORR (CR)	57% (46%)	86% (64%)
Median TTP, mon (range)	11 (2-35+)	14 (2-35+)
2-year OS	76%	93%

Of note, all responding pts to MGd/⁹⁰Y-Zevalin were seen by 4 weeks. Moreover, these data in Rit-Ref FL compare favorably to prior reports with single-agent ⁹⁰Y-Zevalin (ORR 74%, CR 15%, median TTP 6.8 mon- Witzig, 2002) especially in terms of CR rate and TTP.

Conclusion: In conclusion, we found that MGd, when given with ⁹⁰Y-Zevalin, is safe and does not appear to increase hematologic or other toxicity. Furthermore, responses here were prompt with a high rate of durable CR's in Rit-Ref FL (CR 64%, median TTP 14 mon).

018 YTTRIUM-90-LABELED IBRITUMOMAB TIUXETAN (ZEVALIN[®]) FOR PRIMARY CNS LYMPHOMA – FINAL RESULTS OF A PHASE II STUDY

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Introduction: The use of monoclonal antibodies in PCNSL is limited by the reconstitution of the blood-barrier after tumor shrinkage. In this prospective study patients with relapsed PCNSL were treated with a single course of Y-90 anti-CD20 antibody ibritumomab tiuxetan. Penetration of the antibody into the tumor was evaluated by ¹¹¹-Indium-labeled ibritumomab tiuxetan imaging.

Material and Methods: Immunocompetent patients with histologically confirmed, therapy resistant or recurrent PCNSL were treated with rituximab 250 mg/m² on day -7 and day 0, followed by Y-90-ibritumomab tiuxetan 15 MBq/kg IV. In six patients SPECT target imaging with 111-Indium-ibritumomab tiuxetan was performed repeatedly 4-168 hours after Y-90-ibritumomab tiuxetan. Response evaluation by contrast-enhanced MRI was scheduled one month after treatment, every three months thereafter in responders and as clinically indicated.

Results: Ten patients with a median age of 53.5 years (range 41-79) and a median number of 3 (range 1-7) previous therapies were included in the study. A long-term uncertain complete response (uCR) lasting 24+ months was observed in one patient, and an additional three patients had a short-lived response (≤ 1 month). Five patients had disease progression, and one patient did not receive radioimmunotherapy due to prior infection. Leukopenia and thrombocytopenia CTC grade 3/4 were observed in 7 and 8 patients respectively, and pneumonia grade 3/4 in three patients (with fatal outcome in one patient). SPECT indicated target accumulation in the tumor in 4 of 6 patients starting 48 hours and still ongoing 7 days after injection of 111-Indium-ibritumomab tiuxetan.

Conclusions: We provide evidence of Y-90-ibritumomab tiuxetan penetration into PCNSL with target accumulation of the antibody in SPECT. However, responses were mostly of short duration in this heavily pretreated patient cohort with relapses occurring distant of target lesions. Further investigation should include a multimodal approach with chemotherapy and preferably autologous stem cell support.

019 PHASE I/II STUDY OF YTTRIUM-90 LABELED HUMANIZED ANTI-TAC (HAT) MONOCLONAL ANTIBODY AND CALCIUM DTPA IN CD25-EXpressING MALIGNANCIES OTHER THAN ADULT T-CELL LEUKEMIA

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Background: To determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and clinical response in patients with CD25-expressing lymphoid malignancies other than ATL to ⁹⁰Y-HAT.

Methods: Eligibility: Patients (Pts) with T cell malignancies (CD25 staining $\geq 10\%$ of malignant cells) and Hodgkin's lymphoma (HL), Karnofsky performance status (KPS) $>50\%$, AGC $>1,500/\text{mm}^3$, platelet $>100,000/\text{mm}^3$, adequate hepatic/renal function and informed consent. Phase I dose escalation, started at 15mCi ⁹⁰Y-HAT, escalating by 5 mCi until DLT. Pts received ⁹⁰Y-HAT every 6 weeks until disease progression, DLT or completion of 7 cycles. Ca-DTPA was used to reduce bone marrow exposure to free ⁹⁰Y. ¹¹¹In-labeled HAT was used for tumor imaging.

Results: Forty two pts., 8 with cutaneous T cell lymphoma, 2 with peripheral T cell lymphoma, 2 with anaplastic large cell lymphoma, 29 with HL and 1 with chronic lymphocytic leukemia, median age 41 yrs (range, 22-75), median KPS 90% (range, 50-90), all with advanced disease with multiple prior therapies (median 5; range, 1-10) received ⁹⁰Y-HAT every 6-10 weeks. Overall, 112 cycles were administered with a median of 2 (range, 1-7), and mean cycle length 6.5 weeks. The single dose MTD was

15 mCi, with dose limiting thrombocytopenia at 20mCi ⁹⁰Y-HAT. Of 42 pts., 8 (19%) had grade 3/4 thrombocytopenia, 6 (14%) had grade 3/4 anemia and 6 (14%) experienced grade 3/4 neutropenia. After MTD was established, therapy was discontinued in 5 pts due to persistent thrombocytopenia and 2 Pts developed myelodysplastic syndrome. Objective responses have only been seen in the HL Pts; the objective response rate is 63% (13 CR/CRu's, 5 PR's) 6 pts with stable disease and one too early to assess. Median progression free survival is 8 months (range, 1-25) and response duration 6 months (range 1-19+).

Conclusions: We continue to enroll HL patients, as they may represent a particularly favorable group to target with ⁹⁰Y-HAT radioimmunotherapy.

020 RADIOIMMUNOTHERAPY IN NHL AT HIGH CUMULATIVE DOSES OF ⁹⁰Y WITH FRACTIONATED DOSES OF DOTA-CONJUGATED, HUMANIZED ANTI-CD22 IGG, EPRATUZUMAB.

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Background: A phase I/II, multi-center, dose-escalation trial evaluated 2 or 3 weekly infusions of ⁹⁰Y-epratuzumab in patients (pts) with B-cell NHL who had failed ≥ 1 prior standard chemotherapies.

Methods: All pts had $<25\%$ BM involvement, platelets $>100,000/\text{mm}^3$, and measurable disease by CT with no mass >10 cm. The ⁹⁰Y dose was escalated in 3-6 pt cohorts until the occurrence of 2 events of dose limiting toxicity (DLT). Objective responses (OR) and complete responses (CR/CRu) were evaluated by CT-based IWG criteria and response durability by Kaplan-Meier (K-M) analysis.

Results: A total of 64 pts were enrolled with median age 64, 1-7 prior therapies (median 2), and with 77% receiving prior rituximab. Therapy was well tolerated, and other than hematological DLT, without treatment-related grade 3-4 adverse events. The highest total doses achieved were 40 mCi/m² (20 mCi/m² x 2 wk) and 45 mCi/m² (15 mCi/m² x 3 wk). For 58 pts now in the database, OR (CR/CRu) rates increased with total dose [17 pts treated at ≤ 10 mCi/m², 41.2% (29.4%); 12 pts at 15-20 mCi/m², 58.3% (50.0%); 29 pts >20 mCi/m², 72.4% (55.2%)], occurred for all NHL subtypes [31 follicular lymphoma (FCL) pts, 71.0% (58.1%); 14 mantle cell pts, 50.0% (21.4%), 10 diffuse large B-cell pts, 30.0% (30.0%); 3 marginal zone pts, 100% (100%)], and in pts unresponsive to last therapy [17 pts, 71.4% (53.0%)]. For FCL, 18 pts with CR/CRu had durable responses with an estimated median progression free survival now of 16.2 mo., including responses continuing up to 4 years. Preliminary information on the most recent pts (all FCL) indicates 20 mCi/m² x 2 wk dosing is particularly effective (11/11 ORs, 10/11 CR/CRu's).

Conclusion: Fractionated radioimmunotherapy with epratuzumab is feasible and safe, having achieved high response rates at total ⁹⁰Y doses several-fold above the 32-mCi (1200-MBq) limit approved for a single dose of Zevalin.