MAPATUMUMAB (AGONISTIC HUMAN MONOCLONAL ANTIBODY TO TRAIL RECEPTOR-1): REVIEW OF *IN VITRO* AND *IN VIVO* ANTI-LYMPHOMA ACTIVITY

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Two death receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5), expressed in a wide variety of cancer cell types including lymphoma, enable TRAIL (TNF related apoptosis-inducing ligand), a member of the TNF ligand superfamily, to induce apoptosis. Two fully human agonistic monoclonal antibodies, mapatumumab (HGS-ETR1) and lexatumumab (HGS-ETR2), which target and activate TRAIL-R1 or TRAIL-R2, respectively, have been developed which can trigger the extrinsic (mitochondria-independent) apoptotic pathway through these receptors and enhance the anti-tumor effects of chemotherapy drugs in a variety of tumor types, including NHL. Recent work in our laboratory has evaluated the biological effects of rituximab when combined with mapatumumab and lexatumumab on a panel of B-cell lymphoma cell lines. Targeting TRAIL-R1 with mapatumumab can induce apoptosis, cell growth arrest, and in some cell lines, antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CMC). Preclinical in vivo animal studies using mapatumumab demonstrated anti-tumor activity against B-cell neoplasms. The combination of mapatumumab with rituximab resulted in significant synergistic anti-tumor activity. The biological activity of these agonistic TRAIL receptor antibodies does not correlate with the degree of TRAIL-R1 or TRAIL-R2 surface antigen expression. By contrast, although TRAIL-R2 surface receptor was expressed on the B-cell lymphoma cells tested by us and bound by HGS-ETR2 antibody, no significant in vitro anti-tumor activity was observed. These data, in combination with other supportive studies, provided the rationale for conducting a phase 2 multicenter study of mapatumumab in 40 patients with relapsed or refractory NHL. Patients were included on the study if they had relapsed/refractory NHL of any histologic subtype, irrespective of the number of previous treatment regimens. Mapatumumab was administered at 2 dose levels: 3 mg/kg (8 patients) or 10 mg/kg (32 patients) every 21 days in the absence of disease progression or prohibitive toxicity for up to 6 cycles. The primary endpoint was tumor response evaluated by the International Working Group Criteria after every third treatment. Responses were confirmed between 4 and 8 weeks after initial documentation of response. Secondary endpoints included safety and tolerability. The median age of patients was 59.5 years (range 32-81) (24M:16F) with an ECOG performance status 0-2. Patients had received up to 12 previous therapeutic regimens (65% received 3 or more prior regimens) and 94% of patients with B-cell NHL had received rituximab. Histologies included 17 follicular, 9 diffuse large B-cell, 6 mantle cell, 3 peripheral T-cell, 1 marginal zone, 1 small lymphocytic, 1 anaplastic large cell, and 2 lymphomas were not classified. Response data are available for all 40 patients: 3 patients (8%), all with follicular lymphoma, had clinical responses (1CR, 2PR) with duration of response ranging from 9 to 23+ months. Additionally, 13/40 patients (33%) had stable disease, and the remainder had progressive disease at the time of first evaluation. Four patients (follicular) remain on study without disease progression for 17+ to 24+ months. Two patients with a PR continued to receive mapatumumab (12 (relapsed) and 19+ cycles to date). Overall, patients in this study tolerated therapy well. In conclusion, mapatumumab can be safely administered to heavily pretreated NHL patients. Clinical responses were seen in 3/17 follicular lymphoma patients. These data suggest that mapatumumab has activity in heavily pretreated lymphoma patients and further studies in combination with agents active in hematologic malignancies are justified.

THE ROLE OF INTENSIVE CHEMO-IMMUNOTHERAPY IN OPTIMIZING TREATMENT FOR HIGH-RISK LYMPHOMA

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Introduction. The high-dose sequential (HDS) chemotherapy approach is characterized by early dose-intensification followed by autograft with peripheral blood progenitor cells (PBPC). The HDS program was introduced several years ago;[1] subsequently, it has been extensively used in the management of both non-Hodgkin s (NHL) and Hodgkin s Lymphoma (HL).[2-4] Evidence has been then provided that the anti-CD20 Rituximab may improve autograft-based programs, particularly as an in vivo purging agent prior to PBPC harvests.[5-6] Thus, the combined Rituximab-HDS program has been increasingly employed in the management of high-risk B-cell, CD20+ NHL.[7] So far, a large series of lymphoma patients have been treated with the HDS approach at Centers associated to GITIL and their clinical data have been recently collected. Aims of the present study were to evaluate on a large series of high-risk lymphoma patients receiving a HDS treatment: *i.* the long-term outcome; *ii.* the frequency, cumulative incidence and risk factors, of secondary myelodysplasia or acute leukemia (sMDS/AL) development; *iii.* the real benefit of Rituximab addition. *Patients and Methods.* Data have been collected on 1,266 lymphoma patients treated in the last two decades at 10 GITIL Centers. All patients received either the original or modified HDS regimens with autograft; PBPC were usually collected after high-dose (hd)-cyclophosphamide, or, in a subgroup, after a 2nd round of mobilization, with hd-Ara-C.[8] The series included 213 HL and 1,053 NHL patients (630 intermediate/high-grade, 423 low-grade); median age was 46 yrs, 57% were male. Overall, 671 (53%) patients received HDS as salvage treatment after one or more recurrence; 595 (47%) had HDS front-line, either for high-risk clinical presentation or unfavorable histology, i.e. mantle-cell lymphoma. Most patients were autografted with PBPC (median CD34+ cells: 8×10^6/kg), few received BM cells (either alone or with PBPC); 158 (12%) patients did not undergo autograft, due to several reasons, namely: toxicity, disease progression, poor harvests. Among 1,108 autografted patients, a TBI-conditioning regimen was employed only in 79 patients. The value of Rituximab addition was assessed on the subset of 957 B-cell lymphoma patients, who received either the HDS scheme adapted for follicular lymphoma (3) or the hd-Ara-C-supplemented scheme developed for mantle-cell and diffuse large cell lymphoma (4-5). Overall, Rituximab was added to HDS (R+) in 483 (50.5%) patients, the remaining 474 (49.5%) received Rituximab-free HDS (R-). All B-cell lymphoma patients entered the HDS-protocols due to high-risk prognostic features, their median age was 49 yrs., 403 patients (232 R+) had low-grade and 554 (251 R+) had intermediate/high grade B-cell lymphoma subtypes; the intensive program was delivered to 542 (259 R+) patients at diagnosis and to 415 (224 R+) at first or subsequent relapse. *Results. i. long-term outcome.* Overall, 1,013 (80%) patients reached Complete Remission (CR) following the HDS program. Up to now, 93 (7%) patients died for early/late toxicities, 328 (26%) died for lymphoma, 844 are known to be alive; at a median follow-up of 5 yrs, the 5-yr Overall Survival (OS) projection is 64% (s.e. 2%). A significantly higher survival was observed in patients receiving HDS at diagnosis vs. those at relapse and in those achieving CR vs. no CR patients. On multivariate Cox survival analysis, these two parameters maintained a significant impact on the 5-yr survival; also some histological features (low grade vs intermediate/high; B-cell vs. T-cell) had a significant impact on OS, whereas other parameters, including sex, bone marrow involvement, HL vs NHL, use of hd-Ara-C, had no relevance; *ii. sMDS/AL development.* Overall, 38 (3%) patients developed s-MDS/AL, with a cumulative incidence of sMDS/AL of 4.2% at 5 yrs. Median time of s-MDS/AL occurrence was 2.2 yrs since autograft. Several clinical parameters, including age, sex, histology, disease status, BM involvement, were assessed

and found negative for possible association with sMDS/AL occurrence; patients autografted with PBPC of the 2nd round of mobilization had a higher risk of sMDS/AL development compared to those autografted with PBPC of the 1st collection; *iii. impact of Rituximab addition*. In all instances, Rituximab addition was associated with significant improvements; in particular, the 5-yr EFS projections were: 68% for R+ vs. 57% for R- in patients treated at diagnosis and 59% for R+ vs. 34% for R- in patients at relapse; Rituximab addition was of benefit both in low-grade and intermediate/high-grade subtypes. In the Cox multivariate survival analysis, two factors had a significant impact on the EFS, i.e. relapse status at HDS (HR: 1.74, c.i.: 1.43-2.13) and Rituximab addition to HDS (HR: 0.60, c.i.: 0.49-0.75). *Conclusions.* 1. the HDS program including PBPC collection and re-infusion is feasible in a multicenter setting and allows prolonged survival in a good proportion of lymphoma patients presenting with unfavorable prognosis; the long-term outcome is definitely good in patients achieving CR; 2. the incidence of sMDS/AL observed following HDS is among the lowest reported so far in lymphoma patients treated with hd-therapy and autograft; the large quantities of CD34+ cells employed for autograft and the preferential use of TBI-free conditioning regimens might have lowered the risk of sMDS/AL; 3. response and long-term outcome in high-risk B-cell lymphoma patients is markedly improved by the addition of Rituximab to high-dose programs with autograft

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