Haematological malignancies and myeloma

Oral presentations (Mon, 21 Sep, 11:00–13:00)
Haematological malignancies and myeloma

9200 ORAL

Phase II study of IPH1101 (with low dose of IL-2) in combination with rituximab re-treatment in patients with follicular lymphoma

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Background: Non-conventional γδ T lymphocytes have potent anti-tumoral activity, particularly against malignant B cells. IPH1101 is an agonist of γδ T cells, which in the presence of low doses of IL-2 potentiates their direct cytotoxic activity.
ADCC is a major molecular mechanism underlying rituximab's efficacy. Increasing the number and the activation state of killer lymphocytes mediating ADCC is therefore believed to be beneficial for therapeutic potency. Since γδ T cells have been found to be capable of mediating ADCC, modulating γδ T cells in the context of rituximab is worth being tested in a clinical trial. The main purpose is to assess the clinical efficacy of IPH1101 with low doses of IL-2, combined with a standard rituximab treatment, in patients (pts) with follicular lymphoma.
Material and Methods: This is an open label, multinational study consisting of a Phase (ph) I-like part followed by a ph II part. The ph I part has shown a good safety and immuno-biological efficacy profile for the highest dose of IL-2; consequently, the following pts were treated with the combination of rituximab (375 mg/m^2) administered 4 times weekly, IPH1101 (750 mg/m^2) administered i.v. 3 times (every 3 weeks) and IL-2 (8 MIU) administered daily s.c. for 5 days starting on the day of each IPH1101 adm. All pts presented FL which had relapsed after 1 to 4 lines of previous therapy including at least one rituximab-containing line. Inclusion criteria set forth that pts should have no lesion >7 cm.
Results: We report here recent data from the first 15 pts: 3 pts from the ph I part (4 MIU IL-2) and 12 pts at 8 MIU IL-2. Among the 15 pts, 12 were evaluable for efficacy. The safety was good, and most of the drug-related adverse events were, as expected, flu like symptoms of grade 1 or 2. The 4 SAEs reported were hypotension, allergic reaction (back pain), ALAT elevation, and asthenia.The immuno-biological follow up showed specific and sustained γδ T cell amplifications, induction of FcRgIIIa on the targeted γδ T cell population and treatment-induced anti-tumor activity of patients' PBMC ex vivo. After at least 3 months post treatment, investigators reported, among the 12 evaluable pts, 9 responses (75%) of which 6 were CR (50%).
Conclusion: These observations confirm the good safety profile and the biological rationale of this approach. Furthermore, the efficacy in this first set of pts is very promising. The number of CRs is notable and deserves to be confirmed in a larger sample of pts. Updated results will be presented at the meeting.

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Tolerability profile of carfilzomib enables full-dose anti-tumor treatment for up to 12 months

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Background: Carfilzomib (CFZ) is a proteasome inhibitor with single-agent activity against hematologic malignancies, including bortezomib (BTZ)-refractory myeloma (MM) (Jagannath, ASH 2008). CFZ is highly selective and lacks the off-target activities of BTZ (Kapur, ASH 2008). PX-171−004 is an ongoing Phase II study of the safety and efficacy of CFZ in MM patients (pts) with relapsed disease after 1−3 prior therapies. An Overall Response Rate (ORR) of 35.5% for all pts was previously reported (Vij, ASH 2008). Here we present updated safety data on the first 31 pts.
Methods: CFZ 20 mg/m^2 was administered Days 1, 2, 8, 9, 15 and 16 in a 28-day cycle, for up to 12 cycles. Dexamethasone 4 mg was administered prior to each dose in Cycle 1. The primary endpoint was ORR [Partial Response + Very Good Partial Response + Complete Response]. Secondary endpoints included safety.
Results: 31 pts were enrolled; 14 (45%) BTZ-naïve and 17 (55%) BTZ-exposed. Of the BTZ-exposed cohort, 15 (88%) relapsed after stem cell transplantation and 16 (94%) had received at least one IMID-containing regimen. To date, pts have received an average of 6.6 treatment cycles and eleven pts (35%) reached 12 cycles without evidence of disease progression or development of treatment-limiting adverse events (AEs). CFZ achieved an ORR of 57% and 18% in BTZ-naïve and BTZ-exposed pts, respectively. The most common non-hematologic AEs were fatigue (61%), nausea (58%) and vomiting (36%); all were Grades 1/2. Grades 3/4 AEs included neutropenia (10%), anemia (6.5%), upper respiratory infection (6.5%), tumor lysis syndrome (6.5%), dyspnea (6.5%), and thrombocytopenia (6.5%). One report of Grade 3 peripheral neuropathy (PN) occurred in a pt with Grade 1 PN at baseline, attributed to prior thalidomide. The Grade 3 PN resolved to baseline status prior to the pt's final carfilzomib dose. The overall incidence of emergent PN was low (2 pts, 6.5%) despite 73% of pts entering study with a history of PN.
Conclusions: These preliminary results demonstrate that CFZ monotherapy is highly active and well tolerated, with >30% of pts reaching 12 cycles of therapy without evidence of tumor progression or treatment limiting AEs. Importantly, both the rate and severity of PN is significantly lower than reported for BTZ (Richardson, 2006), allowing responding pts to remain on CFZ for at least 1 year without dose modification. These data support the continuing evaluation of CFZ as a promising new agent in relapsed MM.

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Long-term outcomes for patients with limited stage, follicular lymphoma: involved regional radiotherapy versus involved nodal radiotherapy

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Background: Approximately 25% of patients with follicular lymphoma (FL) present with stage I or II disease. Due to the indolent course of FL, it is controversial whether a subset is cured by radiotherapy (RT) alone. Further, it is unclear as to the optimal RT field size to maximize FL control and minimize toxicity. The aim of this study is to review the long-term outcomes of limited stage FL treated with RT alone at the British Columbia Cancer Agency (BCCA). Further, we assess the impact of reducing the RT field size, from involved regional radiotherapy (IRRT) to involved nodal radiotherapy (INRT$\leqslant$5cm), on patterns of relapse and survival.
Methods: Using the BCCA Lymphoid Cancer Database, we identified patients diagnosed with FL between 1986 and 2006. Inclusion criteria were: limited stage (stage I / II, no B symptoms, non-bulky disease <10 cm); grade 1−3A; treated with RT alone with curative intent. Era-specific guidelines for RT were: IRRT, 1986−1998; INRT $\leqslant$ 5 cm, 1998 - present. IRRT was defined as RT to the involved nodal group(s) and $\geqslant$1 adjacent uninvolved nodal group. INRT$\leqslant$5 cm was defined as RT to the involved node(s) with margins $\leqslant$5cm to account for physiological movement and set-up variation.
Results: 237 patients were eligible: median age 61 years; male 48%, stage IA 76%; extranodal disease 23%; elevated LDH 7%; grade 3A 12%; node size $\geqslant$5 cm 19%. The RT groups were: IRRT 142 (60%), INRT$\leqslant$5cm 95 (40%). Median follow-up of living patients was 7.3 years. Median time to relapse was 2.8 years. Only 2 patients relapsed after 10 years. 41% of all patients relapsed: IRRT 45%; INRT$\leqslant$5cm 35%. Distant-only relapse was the most common site of first failure: IRRT 38%; INRT$\leqslant$5cm 31%. Regional-only relapse occurred in only 1% after INRT$\leqslant$5cm. Infield-only relapse was uncommon: 1% in each group. At 10 and 15 years, progression-free survival (PFS) was 49% and 44%; and overall survival (OS) was 66% and 46%, respectively. In multivariate analysis (MVA), larger nodal size ($p = 0.013$), age >60 years ($p = 0.037$) and male sex ($p = 0.044$) were poor prognostic factors for PFS. For OS, age >60 years ($p < 0.001$), elevated LDH ($p = 0.007$), larger nodal size ($p = 0.016$) and grade 3A ($p = 0.036$) were poor prognostic factors. After adjusting for other significant predictors of outcome, the RT groups were not different for OS ($p = 0.328$) or PFS ($p = 0.070$) in final MVA models.

Conclusion: RT alone for limited stage FL is associated with long-term relapse-free survival. Relapse after 10 years is uncommon, suggesting that cure is possible. Reduction in RT field size to INRT≤5cm was not associated with significantly different outcomes.

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Accelerated total lymphoid irradiation (TLI)-containing salvage regimen for patients with refractory and relapsed Hodgkin lymphoma (HL): 20 years outcome with multivariate analysis

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Background: An increasing number of patients with HL fail after receiving chemotherapy alone. We report the long-term results of a program that maximized the benefit of radiotherapy by integrating accelerated involved-field radiotherapy (IFRT) followed by TLI into the high-dose salvage regimen followed by autologous stem-cell transplantation (ASCT).
Materials and Methods: From 11/1985 to 07/2008, 186 previously unirradiated patients with relapsed or refractory HL underwent TLI as part of a high-dose therapy (HDT) salvage regimen prior to ASCT. All were treated on a consecutive series of 4 IRB-approved protocols; 98 (53%) had primary refractory HL, 88 (47%) relapsed after complete response (CR) to chemotherapy alone (58% of those relapsed in <1 year). All refractory or relapsed disease was biopsy proven. Median age at salvage was 30 years. After standard-dose salvage, accelerated IFRT (18−20 Gy) was given to sites of refractory or relapsed disease, followed by TLI of 15−18 Gy and HDT with cyclophosphamide/etoposide. 36% underwent an autologous bone marrow transplantation, 61% a peripheral ASCT, 5 had a double transplant. Overall (OS) and event-free survival (EFS) were analyzed by Cox analysis and disease-specific survival (DSS) by competing risk regression.
Results: With a median follow-up of 57 months, 5- and 10-year OS was 68% and 56%, 5- and 10-year EFS was 62% and 56%, and 5- and 10-year cumulative incidence of HL-related deaths was 21% and 29%, respectively. 116 patients (62%) were alive with no evidence of disease at end of follow-up. On multivariate analysis, CR to salvage chemotherapy predicted for improved OS, EFS and DSS. Primary refractory disease and extranodal disease at relapse predicted for poor EFS. OS improved after introducing peripheral ASCT in 1995 ($p = 0.06$); further improvement was observed following initiation of risk-adapted HDT. Early mortality from ASCT decreased over time ($p = 0.02$); since 1998, only 1 early death from ASCT (1.2%) has occurred. Grade ⩾3 toxicity had no impact on outcome. 8 patients had grade ⩾3 cardiac toxicity; 3 of them died. 11 patients developed second malignancies [AML (2); MDS, DLBCL, NHL, thyroid, lung, stomach, colon, and unknown primary (1 each)]; 5 of them died.
Conclusions: Integrating accelerated IFRT followed by TLI into HDT salvage for previously unirradiated patients with refractory or relapsed HL is effective, feasible and safe. It resulted in excellent long-term OS, EFS and DSS in a heavily pretreated patient population. On multivariate analysis, CR to salvage chemotherapy predicted for improved OS, EFS and DSS.

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Toxicity of high-dose methotrexate (HDMTX) based chemotherapy in primary CNS lymphoma (PCNSL): preliminary experience from a randomized phase III study (G-PCNSL-SG1, NCT00153530)

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Background: The optimal primary therapy for PCNSL has not been defined thus far. This ongoing phase III multicenter study was designed to determine the role of whole-brain radiotherapy (WBRT) after high-dose methotrexate (HDMTX) based first-line chemotherapy. In this preliminary analysis toxicity data for primary chemotherapy are presented.
Patients and Methods: Immunocompetent adult patients with newly diagnosed PCNSL were randomized to consolidating WBRT with 45 Gy (1.5 Gy fractions) or no further therapy in case of complete response (CR) to primary chemotherapy or to rescue WBRT with 45 Gy (1.5 Gy fractions) or high-dose cytarabine in case of non-CR and stratified according to age (< or ⩾60 years) and treating institution. Initial treatment consisted of up to 6 courses HDMTX on day 1 as monotherapy from May 2000 to October 2006, and, from November 2006 according to a protocol amendment, of HDMTX on day 1 and ifosfamide 1.5 g/m^2 over 2h i.v. day 3−5. HDMTX was administered at a dose of 4 g/m^2 over 4h i.v. with an adjustement to creatinine clearance in all patients. Dexamethasone 3×8 g/m^2 was given only in course 1.
Results: At the last evaluation, 498 patients with a median age of 63 years (18−82) and a median Karnofsky Performance Status of 70% (30−100%) evaluable for toxicity have been included. HDMTX alone was given to 394 patients and HDMTX/Ifosfamide to 104 of these patients. Hematologic toxicity was the most common side-effect with leukopenia WHO grade 3−4 in 19.8% (10.7% on HDMTX alone and 54.8% on HDMTX/Ifosfamide; $p < 0.0005$), infections in 20.9% (18.3% on HDMTX alone and 32.7% on HDMTX/Ifosfamide; $p = 0.003$) and thrombocytopenia in 9.7% (8.4% on HDMTX alone and 15.4% on HDMTX/Ifosfamide; $p = 0.041$) of patients. Organ toxicities were infrequent (<10%). Sixty-three (12.6%) patients died on therapy: 12.9% on HDMTX alone and 11.5% on HDMTX/Ifosfamide.
Conclusions: HDMTX based chemotherapy is feasible in a context of a multicenter randomized phase IV study even in older patients when the HDMTX dose is adjusted to creatinine clearance. As expected the combination of HDMTX with ifosfamide was more toxic than HDMTX alone, however, with similar death rate on therapy. At the meeting actualized data will be presented.

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Pralatrexate treatment response by key baseline parameters in the pivotal, multi-center, phase 2 study in relapsed or refractory peripheral T-cell lymphoma (PROPEL)

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Background: The rationally designed antifolate pralatrexate has increased selectivity for cells expressing reduced folate carrier-1 (RFC-1) and is retained within cancer cells for longer time periods due to more efficient polyglutamation by folypolyglutamyl synthase (FPGS). PROPEL (NCT00364923) was an international phase 2 study of pralatrexate in patients (pts) with relapsed or refractory peripheral T-cell lymphoma (PTCL). Overall response rate (ORR) was 27% (29/109) by central review and 39% (42/109) by investigator assessment; median duration of response by central review was 287d. We report here efficacy results in PROPEL by baseline subsets of age, gender, and prior therapy.
Materials and Methods: Pralatrexate 30 mg/m^2 IV was administered weekly for 6 of 7 weeks. Vitamin B_{12} and folic acid were administered to all pts. Eligibility criteria included histologically confirmed PTCL, disease progression after ⩾ 1 prior treatment, and ECOG performance status ⩽ 2. Central reviewers confirmed pathology and assessed response using the International Workshop Criteria (IWC).
Results: 109 pts were evaluable for response. ORR by central review was 31% (12/39) among elderly pts (⩾ 65y) and 24% (17/70) among younger pts (<65y); 27% (20/74) among male pts and 26% (9/35) among female pts; and 26% (6/23), 21% (6/29), and 30% (17/57) among pts with 1, 2, and 3+ prior regimens, respectively. ORR by investigator assessment was 46% (18/39) among elderly pts and 34% (24/70) among younger pts; 38% (28/74) among male pts and 40% (14/35) among female pts; and 39% (9/23), 34% (10/29), and 40% (23/57) among pts with 1, 2, and 3+ prior regimens, respectively. 111 pts were evaluable for safety, including 40 pts ⩾ 65y and 71 pts <65y, and 76 male pts and 35 female pts. Common adverse events by demographic subset (⩾ 65y vs <65y; male vs female) were stomatitis (58% vs 44%; 47% vs 51%), mucosal inflammation (53% vs 28%; 30% vs 51%), and thrombocytopenia (35% vs 28%; 24% vs 46%).
Conclusions: The PROPEL study demonstrated the activity of pralatrexate in pts with relapsed or refractory PTCL. Pralatrexate activity in this study seemed independent of age, gender, or number of prior therapies, with a trend for improved response in the elderly compared to the younger cohort, suggesting pralatrexate may provide a therapeutic option in the management of relapsed refractory PTCL in this age cohort.