major surgery in the treatment of MPM. We reviewed our recent experience among different treatment options in patients with MPM to assess their prognostic impact.
Materials and Methods: From 10/97 to 10/08 326 patients were admitted to our Hospital with a diagnosis of MPM (223 men, 103 women, mean age 64 years, range 32−94). Management options included pleural drainage with/without pleurodesis (24 patients), Video-Assisted Thoracic Surgery (VATS) with/without pleurodesis (195), partial pleurectomy (PL) (27), total PL (8), Extrapleural Pneumonectomy (EPP, 72). The last two treatments were intended as maximal debulking procedures before chemotherapy. Chemotherapy and radiotherapy were used when indicated in exclusive or multimodality protocols. Patients receiving total PL and EPP were compared with those receiving palliative procedures (drainage, VATS or partial PL). Survival analysis was performed using univariate and multivariate (Cox regression) models.
Results: Patients receiving PL (partial or total) and EPP were significantly younger than those receiving pleural drainage or VATS (56 vs. 68 years, $p = 0.002$). Median survival (years) in the different management groups were: pleural drainage (0.97), VATS (0.82), partial PL (1.35), total PL (2.01), EPP (1.73) ($p = 0.00001$). Two-year survival rates among the groups were: pleural drainage 22%, VATS 18%, partial PL 20%, total PL 50%, EPP 32% ($p = 0.00001$). A significant survival advantage was observed in patients receiving EPP or total PL vs. those receiving palliative procedures (32% vs.18%, $p = 0.0002$). In multivariate survival analysis, advanced age was a significant negative prognostic factor (HR 1.02, 95% CI 1.00−1.03, $p = 0.007$), while EPP or total PL were a significant positive prognostic factor (HR 0.59, 95% CI 0.35−0.99, $p = 0.04$).
Conclusions: In patients with MPM, different treatment options may be offered with either palliative or maximal cytoreductive intent. Patients receiving major surgery are a selected subset of patients younger than those receiving pleural drainage or VATS. A significant survival advantage was observed in patients after total PL or EPP. Our results indicate that surgery with maximal debulking intent offers a significant survival advantage over palliative procedures and should therefore be considered a valuable option in selected patients with MPM.

9115 POSTER

Cisplatin-induced expression of Gb3 enables verotoxin-1 treatment of cisplatin-resistance in malignant pleural mesothelioma cells

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Background: Verotoxin-1 (VT-1) exerts its cytotoxicity by targeting the membrane glycolipid Gb3. We investigated if a sub-toxic concentration of VT-1 could enhance cisplatin-induced apoptosis and overcome acquired cisplatin resistance in cultured cancer cell lines.
Materials and Methods: P31 (mesothelioma) and H1299 (non-small-cell lung cancer) cells with corresponding cisplatin-resistant sub-lines (P31res/H1299res) were incubated with VT-1 and/or cisplatin followed by determination of Gb3-expression, cell viability, apoptosis, and signalling pathways.
Results: Cells from the resistant sub-lines had elevated Gb3 expression compared to the parental cell-lines and cisplatin further increased Gb3 expression whereas VT-1 reduced the percentage of Gb3-expressing cells. Combination of cisplatin and sub-toxic concentrations of VT-1 led to a synergistic increase of cytotoxicity and TUNEL-staining, especially in the cisplatin-resistant sub-lines. Blockade of Gb3 synthesis by a Gb3 synthesis inhibitor led to eradicated TUNEL-staining of MPM cells but also sensitized P31res cells to the induction of apoptosis by cisplatin alone. Cisplatin- and VT-1-induced apoptosis involved the MAPK pathways with increased JNK and MKK3/6 phosphorylation.
Conclusions: We demonstrate presence of Gb3 in acquired cisplatin resistance in P31res and H1299res cells. Cisplatin up-regulated Gb3-expression in all cells and thus sensitized the cells to VT-1-induced cytotoxicity. A strong synergistic effect of combined cisplatin and a sub-toxic concentration of VT-1 in cisplatin-resistant MPM cells were noted leading to a potential synergistic clinical treatment approach.

9116 POSTER

A phase I/II clinical trial of topotecan in combination with cisplatin for extensive-disease small cell lung cancer

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Background: *In-vitro* studies have shown synergistic anti-tumor activity between Topotecan (T) and Cisplatin (CDDP) presumably due to inhibition of DNA repair. We conducted a Phase I/II trial to determine a safe and effective combination regimen of T and CDDP in Extensive-Disease small cell lung cancer (ED-SCLC) patients.
Material and Methods: Patients with histologically diagnosed ED-SCLC, Performance Status 0 or 1 and aged 20−74 were enrolled. The combination was constituted at escalating doses of T on consecutive 5 days at 6 dose levels from 0.50 to 1.40 mg/m^2 and fixed dose of CDDP (60 mg/m^2) either on day1 or day5 every 21days. Phase I: We estimated maximum tolerable dose (MTD) in previously treated patients received T and CDDP on day1 and MTD and recommendable dose (RD) in therapy naive patients received T and CDDP on day1 or day5. Phase II: Each 15 therapy naive patients were randomized into two arms (CDDP on day1 or day5 schedules). The RD of T was administered to patients in each arm (step1). In selected CDDP arm, 15 patients from step 1 and an additional 15 therapy naive patients were evaluated for safety and antitumor effect of T and CDDP combination (step2). Preventive G-CSF was administered on day 6 after T administration.
Results: Phase I: 34 patients were enrolled. Both the MTD and the RD of T in combination with CDDP on day1 schedule were estimated as 0.65 mg/m^2. In CDDP on day5 schedule, the MTD and the RD of T were estimated as 1.4 and 1.0 mg/m^2, respectively. Phase II: 30 and 14 patients were enrolled in step 1 and 2, respectively. The response rates (80% for each) were similar for CDDP on day1 and day5 administration schedules. CDDP on day 5 schedule had a better hematological profile (step1). 29 patients with CDDP on day5 schedule yielded 83% response rate (1CR and 23PR, 95% CI, 64.2- 94.2%). Grade 3/4 hematological adverse events were neutropenia (50%), anemia (58.6%) and thrombocytopenia (44.4%). Non hematological adverse events were anorexia, nausea, vomiting, fatigue, alopecia, AST/ALT increase, as dissolved or improved without influence on clinical trial. Hepatic observations were mainly grade 1 and had a tendency of at first or early period. The median survival time in 29 patients on CDDP day5 schedule was 415 days.
Conclusion: The combination of Topotecan on consecutive 5 days and Cisplatin on day 5 schedule with G-CSF support was a safe and effective regimen option for therapy naive patients with ED-SCLC.

9117 POSTER

A phase I study of amrubicin and carboplatin for previously untreated patients with extensive-disease small-cell lung cancer

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Background: Amrubicin and cisplatin are active in the treatment of small-cell lung cancer (SCLC), and carboplatin is an analogue of cisplatin with less non hematological toxicity. However, the appropriate dose of amrubicin and carboplatin combination chemotherapy for previously

untreated patients with extensive-disease (ED) SCLC has not been established.
Purpose: To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of amrubicin and carboplatin in ED-SCLC.
Patients and Methods: Eligibility criteria were chemotherapy-naive ED-SCLC patients, performance status 0−1, age <75, and adequate hematological, hepatic, and renal function. Patients received escalating amrubicin doses under a fixed target AUC 5 of carboplatin (Chatelut formula). Amrubicin and carboplatin were administered by intravenous (i.v.) infusion on days 1, 2, and 3, and day 1, respectively. The initial dose of amrubicin was 30 mg/m^2, and the dose was escalated to 35 and 40 mg/m^2.
Results: Sixteen patients were enrolled and 15 eligible patients were evaluated. One of 6 patients in level 1, 1 of 6 in level 2, and 3 of 3 in level 3 experienced DLT. The presentation of DLTs included neutropenia, leukopenia, thrombocytopenia, febrile neutropenia, and liver dysfunction. The MTD doses of amrubicin and carboplatin were determined as 40 mg/m^2 and AUC 5. Evaluation of responses were 2CR, 9PR, 3SD, and 1PD (response rate 73%), and the median survival time was 13.6 months.
Conclusions: A dose of 35 mg/m^2 amrubicin and carboplatin AUC 5 were recommended. This regimen is associated with an acceptable tolerability profile, and warrants evaluation in the phase II setting.

9118 POSTER

Effect of chemotherapy (CT) in patients (pts) with resected small-cell (SCLC) or large-cell neuro endocrine carcinoma (LCNEC)

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Background: CT and concurrent radiotherapy is the current standard of treatment for limited-stage (LS) SCLC. The role of surgery is limited and remains a matter of controversy. Surgical resection of undiagnosed lung lesion may lead to unintentional removal of SCLC. The benefit of peri-operative CT in resected SCLC or large cell neuroendocrine tumors is unknown.
Material and Methods: This retrospective analysis included LS-SCLC and LCNEC surgically removed between 1979 and 2007 at Surgical Centre Marie Lannelongue. Logrank test was used to compare overall survival.
Results: Among 74 total pts identified, 29 pts (25 male, 4 female, median age of 64 years) underwent surgery (S) and 45 (38 male, 7 female, median age of 58 years) underwent surgery plus chemotherapy (S+C). Four and 21 pts had pre- and post-operative radiotherapy respectively. Pathological diagnosis was as follow: (1) group S: 25 SCLC, 4 LCNEC, 15 pN0 and 10 pN+, and only 2 resections were incomplete (2) group S+C: 34 SCLC, 11 LCNEC, 15 pN0, 27 pN+ and only 3 resections were incomplete. CT was preoperative in 9 pts and postoperative in 37 pts; 62% of the pts received etoposide/platinum, 13% platinum/other agent, 25% other. 15 pts were excluded from the survival analysis, 3 pts alive whose follow-up did not exceed 6 months, 12 pts died within 6 months postoperative, including 4 within 1 month in group S. Among the patients alive at 6 months or followed at least 6 months (n = 59), 33 died, with an overall median follow-up of 5.8 years (range 0.6−19.6). It is 4.5 years (1.4−7) for the group S and 5.8 years (0.6−19.6) for the group S+C. The median survival of the group S (n = 20) and S+C (n = 39) were 2.3 and 6.1 years respectively. The hazard ratio of death was 0.48 (95% CI [0.24–0.99], p = 0.04) for the group S+C compared to the group S. The overall survival at 3 years was 48% in the group S compared to 59% in the group S+C.
Conclusion: These results suggest that peri-operative chemotherapy may be beneficial in pts with resected SCLC or LCNEC.

9119 POSTER

Reciprocal CD4+ T cell balance of Th17 and Treg in small cell lung cancer reflects disease stage

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Background: Small cell lung cancer (SCLC) possesses high tendency to disseminate. However, SCLC patients with paraneoplastic syndrome mediated by immunity against onconeural antigens remain in limited-stage disease (LD) without distant metastases. Cumulative evidence regulates that a balance between immune and regulatory T cells (Treg) determines the magnitude of immune responses to not only self-antigens but also tumor-associated antigens. The purpose of this study was to elucidate the immunological balance induced in SCLC patients.
Materials and Methods: We analyzed T cells in the peripheral blood of 35 consecutive SCLC patients, 8 long-term survivors, and 19 healthy volunteers.
Results: Purified CD4$^+$ T cells with down-regulated expression of CD62L (CD62L^{low}) produced IFN-g, IL-4, and IL-17, thus, considered to be immune effector T cells (Teff). Significantly more Teff numbers were detected in LD-SCLC patients than that of extended-stage (ED) SCLC. By contrast, induction of CD62L^{high}CD25$^+$ CD4$^+$ Treg was significantly higher in ED-SCLC patients. Long-term survivors of SCLC maintained a high Teff to Treg ratio, whereas patients with recurrent disease exhibited a low Teff to Treg ratio. Teff in LD-SCLC patients included more IL-17-producing CD4$^+$ T cells (Th17).
Conclusion: These results show that CD4$^+$ T cell balance may be a biomarker that distinguishes disease stages and predicts recurrence. This study also suggests the importance of inducing effector CD4$^+$ T cells, particularly Th17 cells, while eliminating Treg to control systemic dissemination of SCLC.

9120 POSTER

Second-line amrubicin vs topotecan in extensive-disease small cell lung cancer (ED-SCLC) sensitive to first-line platinum-based chemotherapy: updated results of a randomized phase 2 trial

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Background: Amrubicin (AMR) is a 3rd-generation synthetic anthracycline and potent topoisomerase II inhibitor that has shown an improved early cardiac safety profile relative to other anthracyclines. We compare the efficacy and safety of AMR for 2nd-line treatment of ED-SCLC sensitive to 1st-line chemotherapy with that of topotecan (Topo).
Methods: Randomized, phase 2, open-label, multicenter study (NCT 00319969). Eligible pts had ED-SCLC sensitive to 1st-line platinum-based chemotherapy (recurrence or progression ⩾90 days from completion of 1st-line treatment), ECOG PS ⩽2, and only 1 prior therapy. Pts were randomized (2:1) to IV AMR 40 mg/m^2/d (days 1−3) or IV Topo 1.5 mg/m^2/d (days 1−5) q21 days until progression, unacceptable toxicity, or withdrawal. The primary endpoint was overall response rate (ORR, by RECIST). Secondary endpoints were time to progression (TTP), progression-free survival (PFS), overall survival (OS), and safety. Left ventricular ejection fraction (LVEF) in AMR pts was measured by ECHO or MUGA at baseline (BL), cycles 3, 6, then every 2 cycles, and end of treatment.

Response	AMR (n = 50) n (%)	Topo (n = 26) n(%)
ORR*	22 (44)	3 (12)
CR	6 (12)	1 (4)
PR	16 (32)	2 (8)
SD	11 (22)	10 (39)
PD	13 (26)	9 (35)
N/A†	4 (8)	4 (15)

*AMR vs Topo, p = 0.005; †8 pts (4 each group) discontinued or died before first response assessment.

Results: 76 pts were randomized to AMR (n = 50) or Topo (n = 26). AMR was given for a median of 6 cycles (range 1−16); Topo 3 cycles (1−16). AMR significantly improved ORR vs Topo (p = 0.005 Table), including in older (⩾65 yrs) pts: 46% vs 7%, respectively. Median TTP was 5.6 mos (95% CI 2.8, 6.9) with AMR vs 3.0 mos (95% CI 1.4, 4.4) with Topo. Median PFS was 4.6 mos (95% CI 2.1, 6.1) with AMR vs 3.3 mos (95% CI 2.2, 5.4) with Topo. Median OS was 9.3 mos (95% CI 5.8, 12.2) with AMR vs 7.7 mos (95% CI 4.5, 14.0) with Topo. The most common grade ⩾3 AEs with AMR vs Topo were neutropenia (61% vs 78%), thrombocytopenia (39% vs 61%) and leukopenia (39% vs 39%). Dose reductions were required in