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.

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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.

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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