chemotherapy. With dose-limiting myelosuppression occurred in only HP pts at 700 and 800 and mainly gr 1–2 toxicity at 610, the recommended phase II dose (RD) for HP is proposed at 610. To further define toxicity profile and RD for LP pts, accrual is ongoing at 800. PK at 800 will be available at the meeting. Weekly 1-h infusion of Trabectedin seems to be convenient, active and well tolerated.

551 POSTER

Irofulven (IROF) enhances the antiproliferative effects of oxaliplatin (oxa) in human colon and breast cancer cells

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Background: IROF (6-hydroxymethylacylfulvene, MGI-114) is a novel DNA-interacting anticancer drug derived from the mushroom natural product illudin S. IROF displays activity against human tumors *in vitro* and *in vivo*, and clinical trials as a single agent and in combination with several other anticancer drugs are underway. This study examined the cytotoxicity by combining IROF with OXA, a DACH-platinum compound demonstrating clinical activity in a wide variety of tumors including colorectal cancers. **Materials and Methods:** Drug interaction studies were performed using the Chou & Talalay method in a panel of human colon and breast cancer cell lines. **Results:** Single agent IROF displayed cytotoxicity against human colon cancer HT29 cells (IC50: 1.3±0.2 μg/mL), HT29 IROF-resistant IF2 cells (IC50: 92±9 μg/mL) and human breast cancer MCF7 cells (IC50: 2.0±0.2 μg/mL), HT29 being the most sensitive. In HT29, the OXA-IROF combination led to clear evidence of synergistic activity (Figure 1).

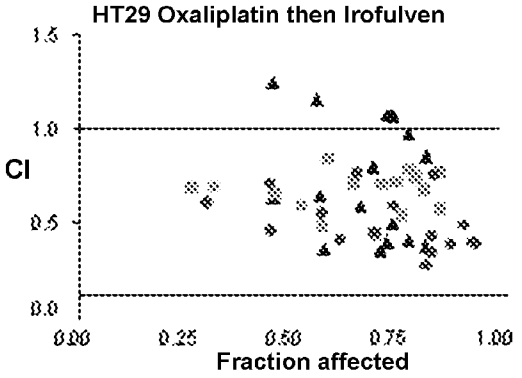

Figure 1. Combination indexes (CI) of IROF-OXA combinations in HT29 colon cancer cells: each spot represents one experiment performed in triplicate (shapes distinguish three separate experiments).

OXA given prior to or after IROF, consistently led to CI<1, demonstrating synergy. Similarly, simultaneous exposure to IROF and OXA was associated with synergy. Similar experiments were done in HT29 IROF-resistant IF2 cells. Acquired resistance to IROF slightly decreased sensitivity in this cell line to the IROF-OXA combination. Additive anti-proliferative effects were observed at low concentration IROF-OXA combinations; whereas, synergy was seen at higher concentrations. From our results, the sequence OXA followed by IROF appears to be the most efficient. To validate the experiments in colon cancer HT29 cells, we explored these combinations in MCF-7 breast cancer cells. In this cell line, additive and/or synergistic effects were observed when OXA was given after or concomitantly to IROF. Only additive effects were observed when OXA was given prior to IROF. **Conclusion:** IROF displays synergistic anti-proliferative effects when combined with OXA over a broad range of concentrations in human colon and breast cancer cells. Acquired resistance to IROF has limited impact on the effects of the combination. Based on these data, the IROF-OXA combination will be further explored in clinical trials, preferably using an OXA prior to IROF schedule.

552 POSTER

Genetic alterations and histology are related to the distinct responses of xenografted gliomas to different alkylating agents

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Background: Response of gliomas to chemotherapy varies widely according to their histological subtype and grade. GBM being resistant while oligodendrogliomas are more chemosensitive. Recent studies showed that, in oligodendrogliomas, the double loss of chromosome 1p and 19q was related to an overall better prognosis. In contrast, several studies have identified genetic alterations related with a poor prognosis, such as EGFR amplification, PTEN mutation or 10q loss, CDKN2A homozygous deletions. Nevertheless, no clear correlation with chemoresistance has been established.
To further study the molecular alterations underlying response to chemotherapy, a series of 12 human gliomas, derived from surgical specimens, was established as xenografts in *nude* mice and used to evaluate *in vivo* the relationship between histology, genetic parameters and response to alkylating drugs generally used in malignant gliomas, BCNU, Carboplatin (CP), Ifosfamide (IFO), and Temozolomide (TMZ).
Material and methods: Of the 12 xenografts used, 8 were high-grade oligodendroglial tumors and 4 were GBM. They were characterized for their genetic alterations, including those considered as "early" alterations, namely chromosome 1 loss +/− chromosome 19q loss, TP53 mutation, and those considered as "late" alterations, namely chromosome 10 loss, chromosome 9p loss, EGFR genomic amplification, PTEN mutation, CDKN2A homozygous deletion and telomerase reactivation. Chemosensitivity to 4 alkylating agents, TMZ {42 mg/kg, d1–5 per os (p.o.)}, BCNU {(5 mg/kg, d1 intraperitoneal (i.p.)}, IFO {90 mg/kg, d1–3, i.p.}, and CP {66 mg/kg, d1, i.p.} was tested.
Results: Although each tumor presented an individual response pattern, GBM had a lower chemosensitivity than oligodendrogliomas and TMZ was the most effective drug. Deletion of 1p+/−19q was associated with higher chemosensitivity, while late molecular alterations, particularly EGFR amplification were associated with chemoresistance.
Conclusions: These results suggest that the combined use of histology and molecular markers should eventually be helpful to select the most appropriate agents in malignant oligodendrogliomas and astrocytomas.

553 POSTER

Activation of trans geometry in bifunctional mononuclear platinum complexes by combining aliphatic and aromatic amines. Mechanistic studies on antitumor action

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The global modification of mammalian and plasmid DNAs by novel platinum compounds, *trans*-[$PtCl_2$(Am1)(Am2)], where Am1 = isopropylamine and Am2 = 3-hydroxymethyl or 4-hydroxymethyl was investigated in cell-free media using various biochemical and biophysical methods. These modifications were analyzed in the context of the activity of these new compounds in several tumor cell lines including those resistant to antitumor *cis*-diamminedichloroplatinum(II) (cisplatin). The results showed that the replacement of both ammine group in clinically ineffective trans isomer of cisplatin [*trans*-diamminedichloroplatinum(II) (transplatin)] resulted in a radical enhancement of its activity in tumor cell lines so that these analogues were more cytotoxic than cisplatin and exhibited significant antitumor activity including activity in cisplatin-resistant tumor cells. Importantly, this replacement also markedly altered DNA binding mode of transplatin. The results offer a strong experimental support for the view that one strategy how to activate trans geometry in bifunctional platinum(II) compounds and to circumvent resistance to cisplatin consists in a chemical modification of the conventional transplatin which would result in their increased efficiency to form in DNA interstrand cross-links. The present work also suggests that such a modification may be accomplished by the replacement of both ammine groups by aliphatic amine ligands, such as isopropylamine and 3-hydroxymethyl or 4-hydroxymethyl. Moreover, the analogues of transplatin apparently represent a novel class of platinum anticancer drugs acting by a different mechanism than "classical" cisplatin.
Acknowledgments
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