1005 POSTER

Indirubin-3'-monoxime, a novel cdk-inhibitor induces cdk-1 and survivin dependent growth arrest and apoptosis in bladder cancer cells.

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Background: In the traditional Chinese Medicine, the preparation Danggui Longhui Wan, has been used for years in treatment of chronic myelocytic leukaemia. The compound, Indirubin, has been shown to be the active constituent. The cell permeable Indirubin-3'-monoxime is a selective and potent inhibitor of cyclin-dependent kinases (CDK).

Material and Methods: In this study we investigated if Indirubin-3'-monoxime can induce apoptosis and tumor cell death in four different bladder cancer cell lines. The growth inhibitory properties were evaluated by EZ4U, a cytotoxic assay; apoptosis induction was determined by immunoblotting of cleaved PARP and flowcytometry of Annexin-V/PI staining during treatment. To evaluate further underlying molecular actions of indirubin-3'-monoxime on the cell cycle, cdk-1 and Survivin, a major apoptosis and mitotic spindle checkpoint-regulating protein were additionally determined by flowcytometry and immunoblotting. Further, we investigated a potential synergism of Indirubin with Paclitaxel, as this drug targets the mitotic spindle and cell cycle regulation, too.

Results: Our results show, that Indirubin-3'-monoxime induces reversible growth arrest in all four cell lines and an increase of apoptosis in two of them. A synergistic effect of a combination of Indirubin-3'-monoxime and Paclitaxel was shown in two cell lines. In the other two, Indirubin competed with Paclitaxel at cdk-1 and abrogated Paclitaxel's cytotoxic efficacy. We found different expressions of cdk-1 and Survivin in the cell lines. These may explain the different behaviour of the cell lines and may help in future to predict the response to the combined therapy.

Conclusions: In summary, Indirubin-3'-monoxime seems a promising candidate for molecular targeted cancer therapy. However, its interaction with other agents needs careful evaluation if given in combination.

Adult leukemia/Lymphoma

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Prognostic value of bone marrow involvement by Hodgkin's disease.

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Background: It has been demonstrated by previous studies that in patients (pts) with Hodgkin's disease (HD) bone marrow (BM) scintigraphy (BMS) is much more sensitive than routine iliac crest biopsy. Unfortunately, prognostic value of scintigraphic data remain undetermined.

Material and method: Since 1992 BMS was performed in 319 pts with HD. Whole body BM visualisation started 45-90 min after i/v injection of 8-10 MBq/kg of 99mTc-colloids. Scintigraphic signs of BM invasion were classified as follows: localised lesions manifested by 1-2 focal defects, generalised involvement - by multifocal (3 and more) defects and diffusely diminished tracer uptake. BM invasion was confirmed by additional examinations (biopsy, MRI, bone scanning, X-ray). Pts with BM invasion underwent combined modality treatment: 6 and more cycles of chemotherapy and radiotherapy of various extent.

Results: BM invasion by HD was diagnosed in 56 cases: localised - in 39, generalised - in another 17 pts. For all 56 pts with BMI 5 year disease free survival was equal to 27% (15/56 pts). Only 2 of 17 pts with generalised BM survived 5 year without HD: DFS - 11%. Five year disease free survival for pts with locolised BM invasion (33%) by HD was 3 times higher than for pts with generalised BM (11%) involvement ($p<0.05$).

Conclusions: Scintigraphic pattern of BM invasion by HD has significant prognostic value: for localised BM invasion 5 year disease free survival is 33%, for generalised - only 11%.

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Accuracy of end of treatment 18F-FDG PET for predicting relapse in patients with Hodgkin's disease (HD) and Non-Hodgkin's lymphoma (NHL)

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Whole-body positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) offers the possibility of differentiating sites of vital tumor from necrotic residual masses. We have previously shown that PET has higher diagnostic and prognostic value than computed tomography in HD and NHL (Jerusalem et al, Blood, 1999; 94: 429-33). The aim of this study was to obtain further information about the accuracy of PET in the end of treatment evaluation of patients suffering from lymphoma. One hundred and eight patients (39 HD, 69 NHL) were recruited prospectively between 5/94 and 10/01. All patients underwent a whole-body PET 1 to 3 months after the end of chemotherapy and/or radiotherapy and had a further follow-up of at least 1 year. Twenty-six patients relapsed (NHL: 23, HD: 3). End of treatment PET was positive in 16/108 (15%) patients. In 12 patients (NHL: 11, HD: 1), PET had correctly identified residual disease (high lesion-to-background ratio: 7 patients, low lesion-to-background ratio: 5 patients) confirmed either by biopsy or by unequivocal conventional imaging studies after a median of 1 (range 0-20) month. In the other 4 patients (NHL: 2, HD: 2), this was a false positive PET. The lesion-to-background ratio was low in 3, suggesting an inflammatory rather than a tumoral lesion, and high in one patient who actually had developed rectal cancer. The 2 of 16 patients with increased ^{18}F-FDG uptake only outside of initial lymphoma involvement were both false positive (1 inflammatory lesion, 1 rectal cancer). Fourteen patients with a negative end of treatment PET relapsed 1-60 months (median: 13.5 months) later. Based on our data end of treatment PET had a sensitivity of 46% (12/26), a specificity of 95% (78/82), a positive predictive value (PPV) of 75% (12/16) a negative predictive value of 85% (78/92) and an overall accuracy of 83% (90/108). These patterns were not different between HD and NHL patients, except that because relapse was a rare event in HD, the impact of false positive PET on PPV value was much more important in HD (PPV: 33%) than in NHL (PPV: 85%). In conclusion, PET is very accurate in predicting short-term treatment failure. However, it cannot detect microscopic residual disease and thus its value is hampered by false negative results in patients later relapsing. On the other hand, a biopsy is always indicated before salvage therapy in order to exclude false positive PET results related to inflammatory lesions or to second primary tumors. All patients with increased ^{18}F-FDG uptake with a high lesion-to-background ratio have either residual tumor or a second primary tumor.

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Randomized trial of accelerated hyperfractionated radiotherapy to 24 Gy versus standard 40 Gy in salvage programs for Hodgkin's disease

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Purpose: To evaluate whether or not low-dose accelerated hyperfractionated radiotherapy (AHFX) is sufficient for control of residual disease compared to standard 40 Gy after salvage chemotherapy (CT) for Hodgkin's disease (HD).

Material and methods: Since September 1999, conventional-dose CT was used in 168 consecutive patients with relapsed or primary refractory HD. Non-cross-resistant CT regimens were changed at each evidence of new progression until achieving systemic control of 6 months duration. If residual disease location was appropriate for full-dose radiotherapy (RT) the patient was randomly allocated either to receive involved-field RT to standard 40 Gy or to 24 Gy in AHFX regimen (1.3-1.5 Gy twice daily with 5 hours interval/24 Gy/8 days). Patients were stratified with regard to chemoresistant (>2 changes of CT regimens required), chemosensitive relapse or primary refractory HD.

Results: Total 92 HD patients were entered on this study. RT was given to 91 sites (79 nodal and 12 bone lesions) in the 66 patients with relapses (53 chemoresistant, 13 chemosensitive). Mediastinal adenopathy was irradiated in the 26 patients with refractory HD; only those with >12 months follow-up were included to this analysis. With a median follow-up of 21 months (range 1-42 months), there were alive and progression-free 26/53 (49%) patients after chemoresistant relapse, 10/13 (77%) patients after chemosensitive relapse and18/26 (69%) of refractory group. No differences were found between the two arms in favor of 40 Gy in any group.