

## The Clinical Benefit of the Histoculture Drug Response Assay

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Gan *et al.*<sup>1)</sup> found a 700-fold difference in doxorubicin sensitivity among bladder cancer histocultures. This indicates great individual variation among patient tumors. Such variations in patients can not be effectively treated by empirical therapy. The clinical studies described below on the histoculture drug response assay (HDRA) indicate its potential survival benefit to patients.

In order to evaluate the histoculture drug response assay (HDRA) with the MTT endpoint for clinical use, chemosensitivity to MMC, doxorubicin, 5-FU and cisplatin of 107 advanced gastric and 109 advanced colorectal cancers were determined *in vitro* in a correlative clinical trial. Of 216 patient specimens, 208 (96.3%) were evaluable in the HDRA. Thirty-eight patients with remaining measurable lesions after surgery were evaluable for comparison of the effects of chemotherapy in the HDRA with clinical outcome. Their overall response in the HDRA to all four drugs correlated to published historical data. Twenty-nine patients were treated with drugs shown to be ineffective in the HDRA and all 29 cases showed clinical chemoresistance. In 9 patients treated with drugs shown to be effective in HDRA, 6 showed clinical chemoresponse and 3 showed arrest of disease progression. The correlations rate of the assay to clinical drug sensitivity response was thus calculated to be 92.1% (35/38), with 100% (29/29) true-negative and 66.7% (6/9) true-positive rates, 100% (6/6) sensitivity, and 90.6% (29/32) specificity<sup>2)</sup>.

Thirty-two patients with stage III and IV gastric cancer without any remaining measurable tumor lesions after surgery were treated with MMC and a fluoropyrimidine adjuvantly. The survival rate of 10 patients whose tumors were sensitive to either MMC and/or 5-FU in the assay was significantly ( $p < 0.005$ ) better than that of 22 patients whose tumors were shown to be insensitive to both drugs. Twenty-nine patients with stage III and IV colorectal cancer without any remaining measurable tumor lesions after surgery were treated with fluoropyrimidines adjuvantly. The recurrence-free survival rate of 7 patients whose tumors were sensitive to 5-FU in the assay was significantly ( $p < 0.005$ ) better than that of 22 patients whose tumors were insensitive. Thus, the HDRA with the MTT endpoint was shown to be of potential clinical use for optimizing chemotherapy and increasing survival<sup>2)</sup>.

To further investigate the potential of the HDRA to contribute to patient survival,

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215 patients with gastric cancer from 45 medical centers were treated with the HDRA in a blinded study after resection of the primary lesion. One-hundred-sixty-eight patients received at least 20 mg/m<sup>2</sup> of MMC and a minimum of 30 g UFT, a mixture of tegafur and uracil at a molar ratio of 1:4, thereby making them eligible for the study. Of these cases, 128 were evaluable in the HDRA. Evaluable patient tumors were tested in the HDRA with the [<sup>3</sup>H]thymidine incorporation endpoint measured by microautoradiography to be drug sensitive or resistant. The *in vitro* conditions for distinguishing sensitivity and resistance that matched the response rates for historical controls for gastric carcinoma were a 90% inhibition rate at 0.12 µg/ml for MMC and a 70% inhibition rate at 1 µg/ml for 5-FU, respectively. Most importantly in the blinded study, the overall and disease-free survival rates of the HDRA-sensitivity group were found to be significantly higher than those of the HDRA-resistant group tested under the same conditions. The results further demonstrated that the HDRA response is correlated to patient survival, which suggested the potential of the HDRA to contribute to cancer patient survival when used prospectively<sup>3</sup>.

A prospective trial was then conducted to determine whether effective agents for each individual patient could be distinguished by the HDRA. Tumor tissues from 30 patients with advanced gastric cancer and 19 with advanced colon cancer were placed in histoculture, treated with chemotherapeutic drugs, and assayed for cell viability with the MTT end-point. Samples from 86% of gastric tumor cases and from 100% of colon tumor cases were successfully cultured and evaluated for chemosensitivity. Patient tumors were scored as sensitive in the HDRA if there was a response to at least one agent. HDRA-sensitive or HDRA-resistant patients were in all other respects clinically indistinguishable. Patients with HDRA-sensitive tumors were treated with the drugs scored as effective in the HDRA while the patients with HDRA-resistant tumors were treated by physician's choice. For patients with gastric cancer, the 50% survival of the HDRA-sensitive cases was 9.8 months compared to the 50% survival of 4.7 months for the HDRA-resistant cases (p=0.02). In colon cancer, the 50% survival in the HDRA-sensitive cases was 16.3 months compared to the 50% survival of 7.4 months for HDRA-resistant cases (p=0.02). This is the first prospective, controlled trial demonstrating an *in vitro* assay that can distinguish those agents effective for survival of the individual cancer patient<sup>4</sup>. The data from these studies demonstrate the clinical benefit of the HDRA for increasing the survival of cancer patients treated with chemotherapy.

## REFERENCES

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