Patients with lower DNA repair capacity are more chemosensitive than those who carry a proficient DNA repair system. More recent results with docetaxel 75mg/m² and cisplatin 75mg/m² yielded a response rate of 31%, with a median survival of 11 months. A meta-analysis of randomised clinical trials comparing cisplatin with carboplatin disclosed that cisplatin doublets yielded 11% longer survival than carboplatin doublets (HR=1.1; p=0.03). The European Organization for Research and Treatment of Cancer (EORTC) compared cisplatin plus teniposide versus cisplatin plus paclitaxel; response rates were significantly in favour of the paclitaxel combination although there were no differences in median survival. Based on this study, the EORTC compared paclitaxel plus cisplatin versus paclitaxel plus gemcitabine versus gemcitabine plus cisplatin. Although there were no differences in outcomes, there was a tendency towards lower survival in the non-cisplatin arm. A Greek study compared docetaxel plus cisplatin versus docetaxel plus gemcitabine; both arms were supported with the use of recombinant human granulocyte colony-stimulating factor, because the dose of docetaxel was 100mg/m². No differences in response or survival were observed. Recent studies of gemcitabine plus docetaxel versus vinorelbine plus cisplatin also show similar outcomes for the two regimens in terms of response and median survival. Along the same lines, a new meta-analysis has found that there are no differences in survival between platinum regimens and third-generation-based non-platinum regimens. One-year survival was 36% for platinum regimens and 35% for non-platinum regimens. At the 2005 ASCO meeting, a phase III trial comparing gemcitabine plus carboplatin versus gemcitabine plus paclitaxel versus paclitaxel plus carboplatin showed similar outcomes for the three regimens, with an overall time to progression of five months, a median survival of eight months, a one-year survival of 33% and a two-year survival of 10%.

Customised Chemotherapy Based on Expression of DNA Repair Genes

In 1995, it was shown that elevated DNA repair capacity is associated with drug resistance in lung cancer cell lines, and it was suggested that modulation of DNA repair mechanisms, such as the incorporation of specific DNA repair inhibitors in therapeutic regimens, could help to improve therapeutic strategies. The overall DNA repair capacity was estimated by the ability of cells to reactivate a plasmid damaged by cisplatin (host cell reactivation assay). Cytotoxicity from cisplatin and other platinum-containing drugs results from the formation of platinum DNA adducts, and clinical outcome is better in patients with higher levels of these adducts, indicating that these patients have lower DNA repair capacity. Nucleotide excision repair (NER) is the major mechanism for repairing platinum DNA adducts, involving the coordinated activity of more than 20 enzymes that remove a segment of DNA containing a bulky adduct, and then restore that segment by replicating the intact complementary strand. The predictive potential of cisplatin adducts in buccal cells was demonstrated in NSCLC patients receiving daily chemotherapy.
Chemotherapy Treatment Options for NSCLC

combined treatment with concomitant cisplatin and radiotherapy. Patients who had higher adduct levels by immunocytochemistry had a median survival of 30 months, in comparison with only five months for patients with low adduct levels. It was hypothesised that patients with genetically determined effective DNA repair activity would be more likely to effectively repair DNA adducts in tumour tissue than patients with genetically determined suboptimal DNA repair. To test this hypothesis, a functional assay of DNA repair capacity – the ability to repair benzo[a]pyrene diol epoxide (BPDE)-induced DNA adducts – in peripheral lymphocytes, rather than in tumours, was used. Median survival was 8.9 months for patients whose DNA repair capacity was in the top quartile, compared with 15.8 months for patients whose DNA repair capacity was in the bottom quartile (p=0.04).

Cisplatin resistance is associated with increased expression of the excision repair cross-complementing 1 (ERCC1) gene. Cancer tissues from ovarian cancer patients whose tumours were clinically resistant to therapy showed greater levels of ERCC1 messenger RNA (mRNA). Complementary DNA (cDNA) derived from primary gastric tumours before chemotherapy was used to determine ERCC1 mRNA levels expressed as the ratio of the polymerase chain reaction (PCR) product of the ERCC1 gene and the β-actin gene. Response and survival with cisplatin plus fluorouracil were significantly associated with levels of ERCC1 ≤5.8. More modern studies have used cDNA derived from paraffin-embedded tumour specimens to determine ERCC1 mRNA expression relative to the internal reference gene β-actin, using fluorescence-based, real time reverse transcriptase PCR. Colorectal cancer patients treated with oxaliplatin plus fluorouracil with low ERCC1 expression had a significantly longer survival compared with patients with high intratumoral ERCC1 mRNA levels. The authors carried out a study to examine the role of ERCC1 mRNA levels in advanced NSCLC patients treated with gemcitabine plus cisplatin. Patients with low ERCC1 mRNA levels attained a response rate of 52%, while in those with high levels, the response rate was 36%. This difference was not significant; however, when a cut-off of 5.8 was used for ERCC1 expression, median survival was 15 months for patients with low levels and only five months for those with high levels (p<0.001).

Based on these findings, an ERCC1 mRNA customised chemotherapy trial was carried out. More than 400 patients have been included and randomised to the control or the experimental arm. The control arm received docetaxel plus cisplatin, and patients in the experimental arm received either the same combination of docetaxel plus cisplatin if their ERCC1 mRNA levels were low, or docetaxel plus gemcitabine if their levels were high (see Figure 1). The preliminary results on 264 patients, presented at ASCO 2005, showed that the response rate for patients with low ERCC1 levels was 56.6% while for patients in the control arm it was 40.4% (p=0.02). When patients in the control arm were split according to the ERCC1 levels, those with low levels had a response rate of 47.3%, while those with high levels had a response rate of 26.1%. The logistic regression model for tumour progression indicated a significant improvement for patients randomised to docetaxel based on low ERCC1 levels. Although the results are still preliminary, time to progression and survival adjusted for age are significantly in favour of the group with low ERCC1 levels.

Figure 1: ERCC1-Customised Chemotherapy in Advanced NSCLC

Figure 2: Adenocarcinoma

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Belani et al. study suggests that paclitaxel stabilisation can prolong survival although the maintenance chemotherapy after partial remission or failure. To date, there has been no clear evidence that maintenance may have some effect on survival.

Maintenance Chemotherapy

To date, there has been no clear evidence that maintenance chemotherapy after partial remission or stabilisation can prolong survival. Although the Belani et al. study suggests that paclitaxel maintenance may have some effect on survival. Intriguingly, the Southwest Oncology Group (SWOG) trial S9504 in stage IIIB showed that the consolidation of three cycles of docetaxel after completion of chemoradiotherapy resulted in an impressive median survival of 26 months. Interestingly, a large study in stage IV disease is being carried out by Schiller et al., where more than 400 patients have received four cycles of gemcitabine plus carboplatin; patients with response or stable disease are then randomised to receive maintenance docetaxel or docetaxel at the time of progression. This study will shed light on the role of tumour DNA repair. It can be speculated that patients with low DNA repair capacity (low ERCC1 or BRCA1 mRNA levels) will obtain better response from gemcitabine plus carboplatin, while they could be potentially resistant to up-front docetaxel. However, these patients could derive the maximum benefit from maintenance docetaxel. It has been observed that cisplatin induces ERCC1 mRNA levels both in pre-clinical models and in the clinical setting. When pre- and post-treatment ERCC1 mRNA levels are looked at, a great variation is observed because cisplatin and other chemotherapeutic agents can induce ERCC1 mRNA expression, which may be a major reason for short-lived response to platinum doublets. This elevation of ERCC1 or associated DNA repair genes can be used to advantage in the later administration of antimicrotubule agents like docetaxel. This hypothesis merits being tested in translational research studies.

EGFR Mutations and DNA Repair Capacity

Recently, EGFR mutations have been found to occur at a significantly higher frequency in hereditary breast cancer than in sporadic breast cancer. The authors have undertaken a prospective study of EGFR mutation assessment in lung adenocarcinoma patients. Dramatic responses have been observed, including brain metastases, with only treatment with tyrosine kinase inhibitors, without the need for radiotherapy or other therapeutic interventions. So far, the data has been collected retrospectively on gefitinib-treated patients after second- or third-line chemotherapy failure. In the authors’ experience, the preliminary evidence of EGFR mutations in lung adenocarcinoma patients in Spain indicates a frequency of 20%. The EGFR assay is performed rapidly with an average wait of five-days for results. Patients without EGFR mutations can be examined to determine their BRCA1 mRNA levels for customised chemotherapy (see Figure 2).
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