Gemcitabine alone or plus cisplatin for biliary tract cancer?

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A randomised phase III trial comparing cisplatin plus gemcitabine with gemcitabine alone for patients with advanced biliary tract cancer has provided evidence for a new standard treatment option for these patients. The therapeutic outcome (overall survival, disease-free survival and disease control rate) was significantly better in the combination arm, with no increase in toxic effects.

Advanced biliary tract carcinoma (ABTC) is a heterogeneous malignant disorder of the digestive tract that has a poor prognosis and is rare in the Western world. Very few treatment options are available for ABTC, owing to a paucity of definitive studies assessing chemotherapy regimens. The rationale for the use of chemotherapy was justified by a study published in 1996 by Glimelius et al.[1], which suggested a survival and a quality of life advantage for patients treated with chemotherapy compared with those who received best supportive care alone.

Numerous small nonrandomised studies of various anticancer chemotherapeutic drugs and combinations of such drugs for ABTC have been published. A pooled analysis of 104 palliative chemotherapy trials in ABTC (a total of 112 trial arms and 2810 patients) reported a tumour response rate of 22.6%, a disease control rate of 57.3%, a median time to progression of 4.1 months, and a pooled overall survival of 8.1 months.[2] Single-agent antimetabolites (5-fluorouracil or gemcitabine) seemed to be more active than other single agents (such as anthracyclines, taxanes and topoisomerase I inhibitors). Furthermore, combined treatments of antimetabolites with platinum salts (cisplatin, oxaliplatin or paraplatin) were superior to other agents and drug combinations.[2] On the basis of these findings, UK investigators initiated a randomised phase II study to compare cisplatin plus gemcitabine with gemcitabine alone, which was subsequently extended to a phase III trial.[3] The study by Valle and colleagues is a pragmatic, well-conducted trial, appreciating the need for multidisciplinary patient management. This trial incorporated biliary stenting in 45% of all patients in both treatment arms. Maintenance of biliary drainage is critical in patients with advanced biliary tract cancer. Aside from the essential quality of life benefit, biliary drainage is a prerequisite for chemotherapeutic drug administration

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.10, and is published with permission. doi:10.1038/nrclinonc.2010.130, www.nature.com/nrclinonc

and counteracts potentially life-threatening biliary sepsis.

Valle and co-workers recruited a total of 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary cancer. These patients were randomly assigned to an outpatient chemotherapy regimen with either cisplatin (25 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 every three weeks, or gemcitabine alone (1000 mg/m^2) on days 1, 8, and 15 every four weeks for up to 24 weeks in both arms.[3] The primary endpoint – a significant improvement in median overall survival with combination chemotherapy compared with gemcitabine alone – was clearly met (11.7 months vs 8.1 months; HR 0.64; $P<0.001$). Similarly, significant increases in the median progression-free survival (8 months vs 5 months; $P<0.001$) and the rate of tumour control (complete or partial response or stable disease, 81.4% vs 71.8%; $P=0.049$) were observed in the experimental arm, importantly with no increase in toxic effects relative to gemcitabine alone. On the basis of these results, the authors conclude that cisplatin plus gemcitabine is an appropriate option for the treatment of patients with ABTC.[3]

These data are consistent with the known preclinical[4] and clinical synergies[5,6] of cisplatin and gemcitabine in other malignancies, such as lung cancer and head and neck cancer, and previous phase I and phase II trials in ABTC.[2] The findings are also supported by the results of a randomised trial involving 83 Japanese patients with ABTC, treated with the same regimens, which were presented at the 2009 ASCO Annual Meeting. That trial reported a median overall survival of 11.2 months in the cisplatin plus gemcitabine group compared with 7.7 months in the gemcitabine-only group.[7] The study by Valle et al.[3] provides an outstanding contribution to the field as it is the very first randomised trial sufficiently powered to define an active treatment regimen in ABTC. Owing to the smaller number of patients and heterogeneous patient population in ABTC as compared with other common malignancies, phase III trials have been a challenge to conduct. The authors have successfully overcome this inherent problem, assisted by an effective coordination of national clinical research efforts. This UK study has not only defined a new standard of care, but also demonstrated that it is feasible to perform large-scale studies in ABTC. Furthermore, despite inherent difficulties in assessing objective response in this disease entity, the authors have succeeded to do so using RECIST criteria. These objective response data were obtainable in at least 74% of their patients who presented with measurable disease (a non-prerequisite for study entry). The findings of this trial also go against previous beliefs that gallbladder cancer and cholangiocellular cancer subgroups vary in the rate of chemotherapeutic responsiveness. For example, Eckel et al.[2] reported a greater likelihood of objective response (36% vs 18%) but inferior overall survival time (7.2 months vs 9.3 months) in patients with advanced gallbladder cancer relative to those with cholangiocarcinoma. The Valle et al.[3] study is in contrast to the rather contradictory findings of this retrospective pooled analysis of previous palliative chemotherapy trials in ABTC.

The biology of biliary tract cancers seems to be in the spectrum of gastrointestinal epithelial cancers with similar oncogenic mutations.[8,9] Key oncogenic mutations in biliary tract cancers include *KRAS*, *EGFR*, and *BRAF*, potentially offering a genetic basis for tailored first-line regimens with targeted agents as has been demonstrated in colorectal cancer.[10] In view of the urgent need for further improvements in the effectiveness of anticancer treatment in ABTC, anti-angiogenic drugs, EGFR inhibitors, inhibitors of BRAF or the downstream MAPK/MEK pathway and other promising novel biologicals warrant investigation. Such testing should be done through well-conducted prospective clinical trials with companion biological exploration to better understand the optimal place of such drugs in ABTC. The study by Valle et al.[3] has been an important contribution for such future trials. The study has firmly established a new classic cytotoxic regimen as standard of care and demonstrated the need and feasibility of coordinated national and international clinical research efforts, which are of paramount importance to continued progress in this field and improved outcomes for our patients.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice points

- The combination of cisplatin plus gemcitabine is an effective palliative treatment option in patients with locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary cancer.
- The demonstration from a randomised phase III trial that cisplatin plus gemcitabine significantly improves disease control rate, progression-free survival and overall survival, with no increased toxic effects compared with gemcitabine alone, confirms this regimen as the new standard treatment for advanced biliary tract carcinoma.

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