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Doxorubicin unnecessary for standard-risk hepatoblastoma

➜ New England Journal of Medicine

Cisplatin monotherapy achieved similar rates of complete resection and survival as cisplatin plus doxorubicin in children with standard-risk hepatoblastoma, a recent trial – SIOPEL 3 – has concluded. As had been predicted, there was less toxicity for patients receiving monotherapy.

The International Childhood Liver Tumour Strategy Group 3 (SIOPEL 3) trial represents a continuation of two earlier trials. In SIOPEL 1, investigators identified two pretreatment prognostic factors – intrahepatic tumour extension and lung metastases – when they administered cisplatin-doxorubicin. Based on these findings, they established two pretreatment risk groups: standard risk (tumour confined to the liver and not more than three hepatic sectors) and high risk (tumours involving the entire liver and beyond). In SIOPEL 2 (a pilot study for the current trial), researchers tried cisplatin monotherapy for the first time, using insights from an earlier trial (*JCO* 2000, 18:2665–2675) that showed a multi-agent anthracycline-free regimen was just as effective as cisplatin-doxorubicin, but with no cardiotoxicity. In the current SIOPEL 3 trial, Giorgio Perilongo and colleagues, from the Department of Pediatrics at the University Hospital of Padua, Italy, set out to answer the question of whether doxorubicin could be safely omitted from the treatment of standard-risk hepatoblastoma, and whether cisplatin alone could be as effective as cisplatin plus doxorubicin. A total of 92 institutions from 24 countries were involved in the study.

Between June 1998 and December 2006, after receiving one cycle of cisplatin (80 mg/m2 body-surface area per 24 hours), children with standard-risk hepatoblastoma were randomised to receive cisplatin (n=126) or cisplatin plus doxorubicin (n=129), administered in three preoperative cycles and two postoperative cycles. Standard risk features were defined as tumours entirely confined to the liver, and involving not more than three hepatic sectors.

During the trial, the protocol was amended, and children with alpha-fetoprotein levels of less than 100 ng/ml were excluded because of "mounting evidence of a poor outcome in these patients," write the authors.

The rate of complete resection was chosen as the primary study endpoint, write the authors, first because it allowed them to obtain meaningful data "regarding the treatment of a very rare tumor in a reasonable time frame," and second "because complete resection is the universally accepted, single most important prognostic factor for long-term overall survival and event-free survival in childhood hepatoblastoma."

The rates of complete resection were 99% with cisplatin and 95% with cisplatin plus doxorubicin, with a difference of 3.9% (95% CI 0.3%–8.1%). The three-year event-free survival was 83% in the cisplatin group and 85.5% in the cisplatin-doxorubicin group, and the three-year overall survival was 95% in the cisplatin group and 93% in the cisplatin-doxorubicin group.

Acute grade 3 or 4 adverse events were 74.4 % with cisplatin-doxorubicin compared to 20.6% for cisplatin monotherapy. No differences in toxicity or nephrotoxicity were detected between the two groups.

"The results of SIOPEL 3 are very encouraging," write the authors. "It has long been known that surgery has an excellent success rate in children with hepatoblastoma and that hepatoblastomas are very sensitive to cisplatin. However, the SIOPEL 3 trial shows that a selected group of patients with hepatoblastoma can be cured with a strategy consisting of cisplatin monotherapy administered preoperatively and postoperatively."

The limited number of patients meant that the authors could not statistically prove their conclusion that the two regimens were comparable. However, the similar rates of event-free survival and overall survival "provide support" for the non-inferiority of cisplatin monotherapy, they argue.

Emerging evidence suggests that few hepatoblastomas with pure foetal histologic features and low mitotic rate seem to be curable by surgery alone, and that small-cell undifferentiated histologic features may have a negative impact on survival, regardless of tumour extension. "Therefore, the conceptualization of future clinical trials should take into account the data from all available trials to refine the appropriate therapy for subgroups of patients with limited-extension hepatoblastoma and to properly balance efficacy and long-term toxicity," write the authors.

■ G Perilongo, R Maibach, E Shafford et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastomas. *NEJM* 22 October 2009, 361:1662–1670

Preserving function when treating brain metastases

➜ Lancet Oncology

Patients with brain metastases treated with stereotatic radiosurgery (SRS) plus whole-brain radiation therapy (WBRT) are at greater risk of a decline in learning and memory function than those receiving SRS alone, a recent study has found. The researchers, led by Eric Chang from the MD Anderson Cancer Centers, in Houston, Texas, conclude that their study supports the use of SRS alone combined with close monitoring as the initial treatment strategy for cancer patients newly diagnosed with between one and three brain metastases.

For more than 50 years WBRT has served as the standard palliative treatment for brain metastases, with randomised trials more recently establishing additional benefits when WBRT is combined with surgery or SRS. Chang and colleagues undertook the phase III randomised trial to test their prediction that the learning and memory function of patients who underwent SRS plus WBRT would be worse than that of patients who underwent SRS alone. "We proposed that memory would be likely to be affected by radiation therapy, given the adverse effects of radiation on neurogenesis of the hippocampus," write the authors.

Between 2001 and 2007, patients with between one and three newly diagnosed brain metastases were randomly assigned to SRS plus WBRT (n=28) or SRS alone (n=30). The researchers measured participants' neurocognitive function using a short battery of neuropsychological tests, where the primary endpoint was changes in the memory function assessed through significant deterioration (5-point drops compared to baseline) in the Hopkins Verbal Learning Test-Revised (HVLT-R) assessment.

Results at four months showed that 52% of patients randomly assigned to SRS plus WBRT showed a significant drop in HVLT-R total recall compared to 24% assigned to SRS alone.

Furthermore, at four months there were four deaths (13%) in the group receiving SRS alone and eight deaths (29%) in the group receiving SRS plus WBRT. The median survival for patients in the SRS group was 15.2 months compared with 5.7 months in the SRS plus WBRT group. After one year, 73% of the surviving patients in the SRS plus WBRT group were free from recurrence, compared with 27% of surviving patients receiving SRS alone.

The trial was stopped at four months in accordance with the predetermined early stopping criteria, which specified that if the probability of one treatment arm being better was greater than 0.975 then the trial should be suspended.

"This study provides level 1 evidence to support the use of SRS alone in the initial management of patients newly diagnosed with one to three brain metastases," write the authors. "We recommend that initial SRS alone combined with close clinical monitoring should be the preferred treatment strategy for such patients."

The recommendation comes despite differences in recurrence favouring joint SRS and WBRT treatment. The risks of learning dysfunction, said the authors, outweighed the benefits of freedom from progression. Nevertheless, patients who opt for SRS alone must be willing to commit to close clinical monitoring afterwards. "Applicability of the findings is dependent on the willingness of patients and their physicians to adhere to a schedule of close monitoring, having consistent access to high-quality MRI, having access to a neurosurgical team willing and able to perform salvage resections when indicated, and applying strict physics quality-assurance procedures for stereotactic radiosurgery," they emphasise.

In an accompanying editorial, Jonathan Knisely from the Yale Cancer Center in New Haven, Connecticut, concludes: "The improvement in both quality of life and survival associated with management by SRS alone show it to be the best approach. Nevertheless, exquisitely detailed MRI studies for planning SRS are crucial for the successful adoption of SRS alone."

■ EL Chang, JS Wefel, KR Hess et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncology* November 2009, 10:1037-1044

■ JPS Knisely. Focused attention on brain metastases. *ibid* pp 1024

Long-term follow-up of adjuvant NSCLC trials

➜ Journal of Clinical Oncology

Two large randomised clinical trials of adjuvant chemotherapy following surgery in non-small-cell lung cancer (NSCLC), published in the same issue of *JCO*, yielded, in the words of editorial writer Jean Yves Douillard, "discordant" results. The International Adjuvant Lung Trial (IALT), at a median follow-up of 7.5 years, showed fading effects for adjuvant chemotherapy on survival; while the North American Intergroup JBR.10 trial, with a median follow-up of 9.3 years, demonstrated that survival benefits were maintained.

The best management of early-stage NSCLC is recognised to be surgical resection with curative intent. However, even with complete resection patients remain at significant risk of relapse and death. Recently, three randomised phase II trials and a meta-analysis have shown significant survival benefit for adjuvant cisplatin-based chemotherapy for selected patients with completely resected stage II and IIIA NSCLC. "Long-term follow-up of patients in these trials is critical to assess whether chemotherapy is associated with a sustained survival benefit and to identify any late toxicities that may be attributable to adjuvant therapy," write the authors of the Intergroup JBR.10 trial.

In the larger, IALT, trial, Rodrigo Arriagada and colleagues, from the Institut Gustave-Roussy in Paris, France, randomly assigned 1867 patients with completely resected NSCLC to three or four cycles of cisplatin-based chemotherapy (n=932) or to observation (n=935). Results at a median follow-up of 7.5 years showed a beneficial effect of adjuvant chemotherapy on overall survival (HR 0.91; 95% CI 0.81–1.02; P=0.10) and on disease-free survival (HR 0.88, 95% CI 0.78–0.98; P=0.02). Furthermore, a significant difference was found for overall survival results before and after five years of follow-up (P=0.006).

"Although the initial benefit during the first five years (reduction of the risk of death) was 14%, after five years, the risk of death was reduced by only 9% with adjuvant chemotherapy and this difference was no longer statistically significant,"

comments Jean-Yves Douillard, from Centre René Gauducheau, (St Herblain, France), in an accompanying editorial.

An analysis of non-lung-cancer deaths for the whole period showed a higher mortality rate in the chemotherapy arm (HR 1.34, 95% CI 0.99–1.81; *P*=0.06. "In the IALT trial, the cumulative lung-cancer-related death rate still favours chemotherapy but an excess of noncancer-related deaths occurred in the chemotherapy arm as compared with the observation arm raising the question of a possible detrimental long-term effect of chemotherapy," writes Douillard.

"This analysis not only confirms a beneficial survival effect of adjuvant cisplatin-based chemotherapy during the first 5 years of follow-up but interestingly shows a significant interaction between the treatment effects according to the duration of follow-up," says Arriagada and colleagues, adding that their findings also raise questions about potential negative long-term effects.

An additional noteworthy finding from the analysis, add the authors, is that a major effect is confirmed in terms of reduction of distant metastases in the chemotherapy arm, with the exception of brain metastases. "If this finding is also reported in other cisplatin-based chemotherapy trials, it would argue for exploration of other potential preventive treatment modalities for patients at high risk of brain failure," they conclude.

In the smaller phase III Intergroup JBR.10 trial, led by Charles Butts from the Cross Cancer Institute in Edmonton, Alberta, Canada, 482 patients with completely resected stage IB or II NSCLC were randomly assigned to receive four cycles of vinorelbine/cisplatin (*n*=242) or observation (*n*=240). At a median follow-up of 9.3 years, results showed patients in the chemotherapy arm continued to experience significant survival advantages compared with patients in the observation arm (HR 0.78, 95% CI 0.61–0.99; *P*=0.04). The absolute improvement in five-year survival was found to be 11% (67% for patients randomised to chemotherapy versus 56% for observation).

Subgroup analysis revealed trends for survival according to disease stage. Patients with stage II NSCLC had a significant benefit in survival from chemotherapy (HR 0.68, 95% CI 0.50–0.92; *P*=0.01), while there was found to be no chemotherapy survival benefit for stage IB patients (HR 1.03, 95% CI 0.70–1.52; *P*=0.87). Within stage IB, however, tumour size was predictive of chemotherapy effect. Patients with tumours 4 cm or larger in size derived clinically meaningful benefit from chemotherapy (HR 0.66, 95% CI 0.39–1.14; *P*=0.13), while those with tumours smaller than 4 cm did not (HR 1.73, 95% CI 0.98–3.04; *P*=0.06). Furthermore, in the JBR.10 trial, the authors found no difference between the groups in the rate of death from other causes or second cancers.

"This updated analysis with more than nine years of follow-up confirms a significant survival benefit for adjuvant chemotherapy in early-stage NSCLC. The survival benefit is seen in the stage II patients. No evidence of unexpected late toxicity or increase in second malignancies from adjuvant chemotherapy was observed," write Butts and colleagues, adding that their study represents the longest reported follow-up data of any of the recent adjuvant NSCLC trials.

Longer follow-up in the adjuvant setting is needed, writes Douillard in his editorial, in order to assess cure. He suggests that the discordant results may in part be accounted for by differences between the two trials, including in the way they defined lung-cancer and non-lung-cancer related deaths, and differences in study patient populations, use of postoperative radiation and types of chemotherapy.

With regards to chemotherapy, the JBR.10 trial used only a single regimen of cisplatin and vinorelbine, while patients in the IALT trial received cisplatin, along with one of four drugs (vindesine, vinblastine, etoposide or vinorelbine).

"The choice of drug to combine with cisplatin may be crucial. To date, vinorelbine is the only third generation drug to demonstrate consistent improvement in survival on a long-term basis," writes Douillard, adding that cisplatin and vinorelbine should be the recommended regimen for a durable and reproducible benefit.

■ CA Butts, K Ding, L Seymour et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR.10. *JCO* 1 January 2010, 28:29–34

■ R Arriagada, A Dunant, JP Pignon et al. Long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. *ibid* pp 35–42

■ JY Douillard. Adjuvant chemotherapy for non-small-cell lung cancer: it does not always fade with time. *ibid* pp 3–5

BRCA1 mutation raises risk of contralateral breast cancer

➜ Journal of Clinical Oncology

The risk of women with inherited forms of breast cancer developing contralateral breast cancer depends on the age they first developed breast cancer and the type of mutations they inherit. In the largest risk estimates study yet of mutations in breast cancer, German researchers showed the risk to be higher for women with *BRCA1* mutations than *BRCA2* mutations.

It is well known that women with *BRCA*-inherited forms of breast cancer are at an increased risk of developing second cancers later in life, often in the opposite (contralateral) breast. Feeling that a more accurate measure of contralateral breast cancer risk was needed, investigators, led by Monika Graeser, from the University Hospital Cologne, Germany, decided to undertake a study investigating patients' individual risks. The research was undertaken by the German Consortium for Hereditary Breast and Ovarian Cancer, an initiative involving 12 university centres which, in 1996, established a large registry to collect comprehensive genotype and phenotype data on families with suspected hereditary breast cancer.

Altogether 2020 women with unilateral breast cancer, entered on the registry between 1996 and 2008, were included in the analysis, comprising 978 index patients and 1042 relatives.

Results showed that 25 years after the first breast cancer, the cumulative risk for contralateral breast cancer was 47.4% (95% CI 38.8%–56.0%) for patients from families with *BRCA1* or *BRCA2* mutations. People from families with *BRCA1* mutations had a 1.6-fold (95% CI 1.2-fold to 2.3-fold) higher risk of contralateral breast cancer than people from families with *BRCA2* mutations.

Younger age at first breast cancer was associated with a significantly higher risk of contralateral breast cancer in patients with *BRCA1* mutations, with a trend observed for patients with *BRCA2* mutations that was not statistically significant. Among patients with *BRCA1* mutations who were younger than 40 years when first diagnosed with breast cancer, 62.9% had developed contralateral breast cancer 25 years on, compared with only 19.6% among those whose first diagnosis came when they were older than 50. Importantly, write the authors, there was no indication that the risk of contralateral breast cancer levelled off within 25 years following first breast cancer.

"To our knowledge, this study is the first to show that patients from families with *BRCA1* mutations face a significantly higher contralateral breast cancer risk compared with patients from families with *BRCA2* mutations," write the authors, adding that the estimated absolute risks in the study were considerably lower than in other studies. "(This) may be of particular clinical relevance for women trying to decide whether to undergo contralateral prophylactic mastectomy at the time of breast cancer diagnosis," they suggest.

In an accompanying editorial, Judy Garber and Mehra Golshan of Brigham and Women's Hospital comment that the data from Graeser and colleagues suggest that surgeons, in particular, should recognise that patients could be mutation carriers, based on age at diagnosis, family history, ethnicity and histologic features, and offer to refer them for genetic testing as appropriate.

At least as important for more mature *BRCA1/2* carriers, they add, is the fact that the study showed the risk of contralateral breast cancer was less compelling for these patients. "There is less justification for contralateral prophylactic mastectomy for this group, and the ordeal of bilateral reconstruction of greater consequence," they write.

■ MK Graeser, C Engel, K Rhiem et al. Contralateral breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. *JCO* December 10 2009, 27:5887–5892

■ JE Garber, M Golshan et al. Contralateral breast cancer in BRCA1/BRCA2 mutation carriers: the story of the other side. *ibid* pp 5862–5864

Home care nursing improves chemotherapy toxicity symptoms

➜ Journal of Clinical Oncology

Home care nursing (HCN) programmes for patients with colorectal and breast cancer receiving oral chemotherapy both improved symptoms and resulted in reduced use of medical services, reports a UK study.

Capecitabine, an orally administered chemotherapy for adjuvant/metastatic colorectal cancer and metastatic breast cancer, produces toxicity in up to 26% of non-pretreated patients and 45% of pretreated patients. An earlier, separate, systematic review had found evidence for the benefits of home care programmes for patients with incurable cancer to be unclear. In the first supportive care randomised trial to test the effects of interventions in patients receiving oral chemotherapy, Alex Molassiotis and colleagues, from the School of Nursing, Midwifery and Social Work at the University of Manchester, UK, set about investigating whether HCN might be a potentially valuable service to offer patients.

In the study, 110 patients with colorectal cancer and 54 patients with breast cancer who were all receiving oral capecitabine were randomly assigned to receive either a home care programme delivered by a nurse, or standard care for 18 weeks (i.e. six cycles of chemotherapy). Standard care consisted of information about the drug and its adverse effects provided by the clinician and accompanied by written information (with patients provided with emergency hotline phone numbers), while the HCN programme included symptom assessment, patient education and/or treatment of symptoms on the basis of agreed protocols, and one standard home visit.

Significant improvements were observed among patients assigned to the home care group for the first four cycles in relation to oral mucositis (P=0.001), diarrhoea (P=0.031), constipation (P=0.002), nausea (P=0.006), pain (P<0.0005), fatigue (P<0.010) and in relation to insomnia for all six cycles (P<0.0005).

Furthermore, although visits to GPs were similar for the two arms, there were significantly lower numbers of calls to the hospital emergency hotline (32 for HCN vs 91 for standard care, P=0.0005) , lower utilisation of other health care services (35 for HCN vs 74 for standard care, P=0.008) and lower numbers of inpatient days in the home care group (57 for HCN vs 167 for standard care, P=0.02).

"An HCN, symptom-focused intervention appears to be an effective way of supporting patients," write the authors, adding that although this may not be feasible for large numbers of patients who receive oral chemotherapy, resource savings in other areas of health care utilisation might offset the HCN costs.

Improvements in toxicity were most evident in the first two cycles of chemotherapy (i.e. the first six weeks), supported by both the single toxicity score and the analysis of each individual symptom. "This suggests that the most crucial time to provide a supportive care intervention in patients receiving capecitabine is during the first two cycles of treatment. Although patients generally receive information and education about their chemotherapy before starting treatment, they may feel overwhelmed with such information, and re-education and support during the first few weeks of treatment seems an appropriate and useful approach. Also, such an intervention maintains better continuity of care and a more positive experience of treatment," write the authors, adding that the generic approach to symptom management makes this intervention appropriate for other oral chemotherapies.

■ A Molassiotis, S Brearley, M Saunders. Effectiveness of a home care nursing program in the symptom management of patients with colorectal and breast cancer receiving oral chemotherapy: a randomized, controlled trial. *JCO* 20 December 2009, 27:6191–6198