Which questions remain unanswered following the successful development of sorafenib in hepatocellular carcinoma?

➜ Keith Flaherty and Weijing Sun

In patients with advanced hepatocellular carcinoma who have a good performance status and Child–Turcotte–Pugh class A liver function, sorafenib represents a new standard of care.

Summary

Investigation of the effects of various antiangiogenic agents in the therapy of solid tumours has been a dominant theme in oncology for the past decade. Hepatocellular carcinoma has joined the short list of tumour types for which single-agent antiangiogenic therapy has shown clear clinical benefit. Here we discuss the findings of a multicentre, phase III trial by Llovet et al. (**Sorafenib in advanced hepatocelluar carcinoma**. *N Engl J Med* 359:378–390), which compared overall survival, time to symptomatic progression and time to radiologic progression in patients with hepatocellular carcinoma who received either sorafenib or placebo. Patients treated with sorafenib had approximately three months longer overall survival and time to radiologic progression than patients who received placebo. Elucidation of tumour-specific and patient-specific factors that identify which patients with hepatocellular carcinoma will derive greatest benefit from antiangiogenic therapies such as sorafenib is of critical importance.

This article was first published online in ***Nature Clinical Practice Oncology*** 17 December 2008, and is reproduced with permission.

Hepatocellular carcinoma (HCC) is one of the world's major health problems, with 500,000 new cases diagnosed per year worldwide and a rising incidence in the US and Europe. The challenge in treatment of advanced disease is twofold: lack of effective agents and limited treatment efficacy owing to the underlying liver dysfunction. Preclinical data demonstrate that antiangiogenic agents, including sorafenib and bevacizumab, have efficacy in HCC cell lines and xenograft models.[1]

Sorafenib targets a wide spectrum of kinases that are active in disease pathways, including c-Raf, VEGF and platelet-derived growth factor beta (PDGF β). The primary mechanism of action of sorafenib has been difficult to discern in some tumour types during clinical trials of this drug. Sorafenib inhibits tumour angiogenesis in human tumour xenografts, although the specific target or targets involved cannot be conclusively stated.

Two critical observations have been made on the HCC trials conducted with sorafenib. Bevacizumab, a monoclonal antibody that exclusively targets VEGF, was evaluated in several phase II trials alone and in combination with chemotherapy in HCC. While no phase III data have yet demonstrated a survival benefit with bevacizumab in HCC, the phase II trials suggest that

such a benefit exists.[2–4] These data support the hypothesis that the inhibition of VEGF signaling achieved with sorafenib might contribute significantly to its activity in HCC. On the other hand, Abou-Alfa and colleagues noted a correlation between high tumour MAP kinase (MAPK) pathway activity and prolonged progression-free survival in response to sorafenib.[5] As this study lacked a control group, a definitive conclusion is not possible that activation of this pathway represents a useful predictor of response; however, the available evidence suggests that high MAPK activity is an adverse prognostic feature. Thus, the association between high MAPK pathway activity and good clinical outcome in patients with high intrinsic MAPK activity who responded well to sorafenib suggests that the drug exerts some effect on this pathway, presumably at the level of Raf. Therefore, sorafenib might exert an influence on both VEGF-mediated angiogenesis and MAPK pathway activity in the context of HCC.

The regulatory authorities in the US and Europe approved sorafenib for the treatment of advanced HCC on the basis of data from a large, randomised, double-blind, placebo-controlled, phase III study (SHARP).[6] The study included 602 patients with advanced HCC from 121 centres in 21 countries in Europe, North America, South America and Australia who were ineligible for, or who experienced disease progression after, surgical or locoregional therapies. Other key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, Child–Turcotte–Pugh class A liver function, life expectancy more than 12 weeks and adequate haematologic, liver and renal function. Patients who had received molecularly targeted or other systemic therapies were excluded. After randomisation, patients were given either 400 mg sorafenib twice daily (n=299) or a matching placebo (n=303). The median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR 0.69, range 0.55–0.87; P<0.001). Notably, most patients had a good performance status and preserved liver function, which is not usually seen in general oncology practice: 54% of patients had an ECOG performance status of 0, 38% had an ECOG performance status of 1, and 95% of patients had Child–Turcotte–Pugh class A liver function. Data are lacking for patients with relatively advanced liver failure (Child–Turcotte–Pugh class B or C) and poor performance status (ECOG score >2). Since the SHARP trial population was predominantly European and only a small proportion had hepatitis B virus as the causative factor, a second phase III study was conducted to verify the role of sorafenib in Asian patients with HCC, among whom hepatitis B viral infection is the predominant causative factor of advanced disease (75%).[7] The benefits of sorafenib mirrored those in the SHARP trial with respect to the survival advantage (HR 0.67, range 0.49–0.93; P=0.0155), but both groups had inferior outcomes compared with SHARP trial participants (median overall survival 6.5 months and 4.1 months for the sorafenib and placebo groups, respectively). Although the Asian cohort had more advanced disease, these results suggest that sorafenib might offer greater benefit in hepatitis C virus-infected patients than in other aetiologic subgroups of HCC, an observation that deserves further investigation. Another provocative result comes from a phase II, randomised study that showed potential benefit for the combination of sorafenib and doxorubicin compared with doxorubicin alone (median overall survival 13.8 months vs 6.5 months; P=0.0129).[8] These results, however, must be interpreted carefully as the sample size was small and the combination therapy was associated with increased cardiac toxicity (left ventricular dysfunction 19% vs 2%).

After a decade's efforts, sorafenib is the first agent to demonstrate a survival benefit in the treatment of advanced HCC. The primary mechanism of action of this agent remains uncertain, but inhibition of both angiogenesis and the MAPK pathway seem to have a role. An improved clinical effect might be obtained by using combinations of drugs that target angiogenesis and MAPK signaling, and this strategy could form the next generation of trials that combine sorafenib with other targeted therapies. Caution should be applied when sorafenib is considered for patients with HCC and advanced liver failure. Such patients were not included in the phase II or phase III trials and they might not tolerate sorafenib as well as those with preserved liver function. More studies are needed in this population of patients.

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

Competing interests: Keith Flaherty declared associations with Bayer and Onyx Pharmaceuticals. See the article online article at www.nature/clinicalpractice for full details of the relationship

Keith Flaherty is an assistant professor of medicine and Weijing Sun is an associate professor and director of gastrointestinal medical oncology, both at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

How does extended lymphadenectomy influence practical care for patients with gastric cancer?

Ilfet Songun and Cornelis van de Velde

A recent study showed no benefit from extending lymphadenectomy beyond D1+ in gastric cancer. Adequate lymphadenectomy at high-volume institutions is essential for locoregional control and survival in this group of patients.

Summary

The recurrence and survival rates in patients with curable gastric cancer remain suboptimal. Debate on the optimal extent of lymphadenectomy for the surgical treatment of these patients is, therefore, still ongoing. A randomised, controlled trial by Sasako et al. (**D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer**. *N Engl J Med* 359:453–462) examined whether addition of para-aortic nodal dissection to D2 lymphadenectomy improves survival in patients with gastric cancer. The results from this trial, whose primary endpoint was overall survival, demonstrated no additional benefit of lymphadenectomy beyond D2 resection. Management strategies should focus on optimal lymphadenectomy in high-volume hospitals, with evaluation of chemotherapy and radiotherapy, to achieve low surgery-related morbidity and mortality, optimal locoregional control and improved survival rates for patients with curable gastric cancer.

This article was first published online in ***Nature Clinical Practice Oncology*** 17 December 2008, and is reproduced with permission.

The extent of lymphadenectomy required to achieve locoregional control in gastric cancer has been debated for over two decades, and the discussion is still ongoing. Radical lymphadenectomy did not increase long-term survival after curative surgery in either the Dutch Gastric Cancer Group (DGCG) trial[1] or in the Medical Research Council (MRC) trial.[2] Wu et al. demonstrated improved survival for patients with gastric cancer treated with curative resection in a single-institution randomised trial after D3 lymphadenectomy compared with D1 lymphadenectomy.[3] In this study, however, D3 dissection did not result in removal of a greater number of positive nodes than D1 dissection did. The choice of overall survival as the primary endpoint in this study was questionable because 15% of deaths were not tumour-related, which reduced the observed difference between the groups in disease-specific survival.[3]

The study by Sasako et al. is one of the most recent to address the issue of the extent of lymphadenectomy in gastric cancer.[4] This trial was designed to detect an overall five-year survival benefit of 8%, and 523 patients (maximum age 75 years) with stage T2b, T3 or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (D2; *n*=263) or D2 lymphadenectomy together with para-aortic nodal dissection (D2–PAND; *n*=260). The inclusion period was approximately

six years with 24 participating centres in Japan. The primary endpoint of the study was overall survival and the secondary endpoints were recurrence-free survival, surgery-related complications and hospital death. Rates of surgery-related complications in the D2-only and D2–PAND groups were 20.9% and 28.1%, respectively (P=0.07). Mortality from any cause within 30 days after surgery was 0.8% in both groups. In the group assigned to D2–PAND, the median operative time was 63 minutes longer and the median blood loss was 230 ml greater than in the D2-only group. The five-year overall survival rates were 69.2% and 70.3% in the D2-only and D2–PAND groups, respectively. For patients treated with D2–PAND, the hazard ratio for death was 1.03 (P=0.85). No significant differences in recurrence patterns or recurrence-free survival were observed in the two groups. Two-thirds of the patients (n=348) had positive nodes, but only 8.5% (n=22) had positive para-aortic nodes, which is a small number to address the question of whether D2–PAND results in better survival compared with D2 alone. No significant difference was apparent in the number of positive nodes in the two treatment groups. D2–PAND did not improve the overall five-year survival of patients with positive para-aortic nodes. The overall survival of node-positive patients (n=348) was better in the D2-only group (65.2%) than in the D2–PAND group (54.9%, P=0.04), although the overall survival of node-negative patients (n=174) was better in the D2–PAND group (96.8%) compared with the D2-only group (78.4%; P=0.009), which we think is a surprising finding.

The authors conclude that D2 plus PAND does not improve survival of patients with curable gastric cancer, and that D2 lymphadenectomy should be performed in high-volume institutions with sufficient experience in this procedure and its postoperative management. Even though the operative mortality and overall five-year survival rates reported by Sasako et al. are impressive, the strict inclusion criteria make the results of this study not directly translatable to the general population. The authors criticise the DGCG and MRC trials because of the surgeons' limited experience of extended lymphadenectomy procedures, and the suboptimal capability of the hospitals to manage major surgical complications owing to their low numbers of cases. These trials, however, reflect what is achieved in terms of survival in the general population, better than Sasako et al.'s study. Regardless of variation in nodal dissections, no significant difference in overall survival between D1 or D2 surgery was observed in the DGCG and MRC trials.[1,2] An autopsy-based analysis of patterns of failure with respect to the Maruyama index (MI) of 441 deaths that occurred in the DGCG trial demonstrated that isolated regional failure (8% in those with MI <5 vs 21% in those with MI ≥5) and combined regional and distant failure (19% for the MI <5 group vs 36% for the MI ≥5 group) occurred less frequently in the MI <5 group (P<0.001).[5]

MacDonald et al. assessed the effect of surgery plus adjuvant chemotherapy and radiotherapy on survival of patients with resectable gastric cancer.[6] Only 10% of the patients had the recommended D2 lymphadenectomy and 54% had a D0 lymphadenectomy; three-year survival in the combined therapy and surgery-only groups was 50% and 41%, respectively (P=0.005). In the surgery-only group, 64% of patients had relapses versus 43% of patients in the combination-therapy group (P<0.001).[6] The authors concluded that postoperative chemotherapy and radiotherapy significantly improves overall and relapse-free survival, and should be considered for all patients at high risk for recurrence after curative resection, such as patients who have had D0 or D1 lymphadenectomy.[6]

Sasako et al. demonstrate that lymphadenectomy beyond D2 does not improve locoregional control.[4] Radical surgery seems to have reached the limit of its benefit. Unfortunately, increased morbidity and mortality associated with D2 lymphadenectomy highlight that this is still a high-risk procedure. Gastric cancer treatment in high-volume institutions should focus on implementing high-quality care (i.e. in anaesthesia, surgical technique, nurse staffing and training). Low-volume institutions should monitor the completeness of resection, adequacy of lymph-node examination and their participation in clinical trials to reduce the risks of postoperative morbidity and mortality associated with gastric cancer surgery, and to improve locoregional control and survival.[7] Other key issues that still need to be addressed are whether patients with a low MI will derive a survival benefit and improved locoregional control from chemotherapy and radiotherapy combined with surgery and optimal lymphadenectomy (i.e. ≥15 lymph nodes removed) without splenectomy. These issues are currently being addressed in the Dutch CRITICS randomised trial, the results of which are anticipated in eight years.

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

Ilfet Songun is a surgeon at the Department of Surgery, Slotervaart Hospital, Amsterdam, and Cornelis van de Velde is professor of surgery at the Department of Surgery, Leiden University Medical Centre, The Netherlands