Clinical implications for cediranib in advanced cervical cancer

For decades, the management of women with recurrent or persistent cervical cancer not amenable to surgery and women who present with metastatic disease has constituted a high unmet clinical need, with platinum-based chemotherapy being palliative and associated with short-lived responses, rapid deterioration in quality of life, and early death (median overall survival 7–12 months).[1] Some progress has been made following the publication of the phase 3 randomised Gynecologic Oncology Group (GOG) 240 trial;[1] patients who received the anti-angiogenic drug bevacizumab in addition to chemotherapy had a significant overall survival advantage over those who did not (median 17 months *vs* 13·3 months; HR 0·71 [98% CI 0·54–0·95]; p=0·004). In addition to overall survival, both progression-free survival (median 8·2 months *vs* 5·9 months) and the proportion of patients who achieved an objective tumour response (48% *vs* 36%) were significantly improved with the combination of bevacizumab with either of two chemotherapy doublets (cisplatin–paclitaxel or topotecan–paclitaxel).[1] None of these findings were accompanied by a significant deterioration in quality of life.[2] These results led directly to the approval of bevacizumab by the US Food and Drug Administration and the European Medicines Agency.

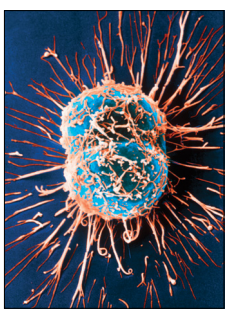
In *The Lancet Oncology*, Paul Symonds and colleagues[3] report the results of the randomised phase 2, double-blind, placebo-controlled CIRCCa trial. The authors report significantly improved progression-free survival with six cycles of carboplatin–paclitaxel plus daily administration of cediranib, continued until disease progression or the development of intolerable toxicity (hazard ratio 0·58 [80% CI 0·40–0·85]; p=0·032).[3] Cediranib, a VEGFR1–3 oral tyrosine kinase inhibitor, joins TNP-470,[4] pazopanib,[5] and bevacizumab[1,6] as an anti-angiogenic drug with demonstrable activity in cervical cancer, with the latter two drugs also inhibiting VEGF-dependent signalling.[7] Although this trial was not powered to assess overall survival, the proportion of patients with a response (64%) in the cediranib group is the highest reported for any regimen in this disease.[3]

The use of carboplatin in CIRCCa deserves comment. Although the Japanese Clinical Oncology Group (JCOG) have shown significant non-inferiority of carboplatin in JCOG 0505, a phase 3 randomised trial comparing cisplatin–paclitaxel with carboplatin–paclitaxel, they also reported that in patients who had never received platinum treatment, the cisplatin–paclitaxel treatment was superior.[8] Although the carboplatin–paclitaxel doublet is certainly easier to administer than cisplatin–paclitaxel, caution should be exercised in women who have not previously received any platinum-based therapy (eg, those treated with radiotherapy alone for locally advanced disease and those who present with FIGO IVB tumours), and also in elderly patients and those previously treated with extended-field radiation for whom carboplatin could prove to be intolerable owing to vastly diminished bone marrow reserves.

Unlike in GOG 240, febrile neutropenia was an important problem in CIRCCa.[1,3] In addition, diarrhoea induced by cediranib significantly affected one quality-of-life measure (p=0·030).[3] Finally, although the authors indicate that cross-trial comparisons are rarely valid, treatment-induced grade 2 or greater hypertension (34% in CIRCCa *vs* 25% in GOG 240) might indicate that this side-effect is a greater problem with cediranib than with bevacizumab.[1,3] By contrast, cediranib was not associated with the development of fistulae—a disorder that occurred in 8·6% of patients treated with chemotherapy plus bevacizumab in GOG 240.[1,3]

Although at quite an early stage in its life cycle, cediranib has already had an interesting history. An absence of perceived benefit in colorectal cancer, lung cancer, and glioblastoma curtailed enthusiasm for further development until the results of CIRCCa and the ICON6 ovarian cancer study were made available. Importantly, ICON6 represents one of eight pivotal phase 3 anti-angiogenesis trials in ovarian cancer, all of which met their primary endpoint (progression-free survival), with ICON6 being the only study to show an overall survival advantage.[9] Stalled development of cediranib had implications for CIRCCa, but fortunately development of the drug has since been resurrected to focus on gynaecological malignancies.

Similarities in eligibility criteria between CIRCCa and GOG 240 (eg, ECOG performance status restricted to 0–1 and no previous chemotherapy allowed for recurrent disease) suggest that a correlation of the progression-free survival results might be reasonable (ie, 8·1 months in CIRCCa is similar to 8·2 months in GOG 240).[1,3] Cost-effectiveness remains an issue,[10] especially for low-income nations where the incidence of cervical cancer is highest.



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Given a new treatment standard of chemotherapy plus bevacizumab, where to position cediranib is not readily discernible. Potential future trial designs might use strategies to study chemotherapy plus bevacizumab with and without cediranib, or randomisation to cediranib maintenance therapy in patients who derive clinical benefit from chemotherapy plus bevacizumab (eg, stable disease). If active as a monotherapy, a maintenance strategy containing cediranib could have major toxicology implications given that the median duration of cediranib treatment in both groups in CIRCCa was 19 weeks and overlapped with chemotherapy. Clearly, the results of CIRCCa provide additional clinical evidence that VEGF-dependent tumour angiogenesis remains a valid target in cervical cancer and that the need to explore novel anti-angiogenesis combinations and sequencing is implicit.

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I have participated on two advisory boards for Genentech/Roche (March, 2014, and July, 2014). I declare no other competing interests.

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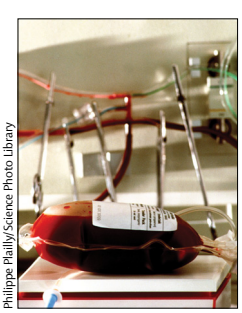
Busulfan-based conditioning regimens: not all partners are equal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Since its introduction in 1987, the combination of busulfan and cyclophosphamide has been the most frequently used non-total body irradiation-containing myeloablative regimen for acute myeloid leukaemia throughout the world.[1] With the introduction of fludarabine-containing reduced conditioning regimens, many investigators replaced the cyclophosphamide with fludarabine in an effort to reduce the toxic effects that were thought to be caused by cyclophosphamide metabolites.[2-4] The busulfan plus fludarabine regimen has become increasingly popular, and although multiple retrospective comparisons have reported that the combination of busulfan and fludarabine is less toxic and compares favourably with the classic busulfan plus cyclophosphamide regimen, only two randomised trials[5,6] have been done, with conflicting results. Both trials were hampered by sample size and patient heterogeneity.

In *The Lancet Oncology*, Alessandro Rambaldi and colleagues report the results of a multicentre, randomised trial done through the Gruppo Italiano de Trapianto Midollo Osseo (GITMO) network, which compared busulfan plus cyclophosphamide with busulfan plus fludarabine.[7] The trial was restricted to patients with acute myeloid leukaemia aged older than 40 years. 252 patients were randomly assigned to receive intravenous busulfan (12·8 mg/kg), in combination with cyclophosphamide (120 mg/kg) or fludarabine (160 mg/m^2). 1-year non-relapse mortality was 17·2% (95% CI 11·6–25·4) in the busulfan plus cyclophosphamide group compared with 7·9% (4·3–14·3) in the busulfan plus fludarabine group (p=0·026), and this difference remained significant even at 2 and 5 years after transplantation. However, no significant difference existed in 5-year leukaemia-free survival between the two groups (42·9% [34·4–53·6] for busulfan plus cyclophosphamide *vs* 51·8% [43·6–61·7] for busulfan plus fludarabine; p=0·29). 1-year cumulative relapse was similar between groups (22·1%