Editorial

Chemotherapy for Cervical Cancer

Globally cervical cancer is the second most common cancer among women; approximately 80% of total cases occur in developing countries.[1] The prognosis of this disease is directly related to the stage at presentation. Surgery or radical radiotherapy (RT) in the early stages of disease (stage IA-IIA) results in cure in more than 80% of women For advanced disease (IIB-IVA), five year survival rate is 60% for stage II B, 30-35% for stage III and <15% for stage IV A disease following radiotherapy. Loco-regional recurrence (seen in 40% to 70% of patients) is the main cause of failure post radiation. 20% patients fail due to distant metastasis. Chemotherapy has been used during past 3 decades for the treatment of recurrent or metastatic disease. Cisplatin and ifosphamide are two most active agents. About 30% of patients respond to cisplatin with achievement of complete response in less than 10%. Patients in good performance status (ECOG,0-2) , and those with normal renal functions tolerate chemotherapy better. Patients with extra-pelvic disease respond better than those with pelvic recurrence.[2] Compared to single agent cisplatin, the response rates with combination chemotherapy are higher, however, survival is not significantly different.[3]

A number of investigators have explored the role of chemotherapy in the primary management of locally advanced (stage IIB-IVA) cervical cancer. Initial studies used chemotherapy prior to radiotherapy or surgery (neoadjuvant, NACT). Five randomized studies (reviewed in ref. 4) have examined the role of NACT chemotherapy given prior to RT compared to RT alone. Following chemotherapy, response rates ranged from 43-80% with complete response (CR) in 0 to 22% of patients. With subsequent RT, approximately, 65% of patients (range 43% to 75%) achieved clinical CR. These response rates were similar to those achieved with RT alone (median 67%, range 32-92%). Despite the significant responses achieved with NACT and improved survival for chemotherapy responders compared to chemotherapy non -responders, the overall survival for patients receiving NACT – RT was not improved in a meta analysis of individual patients data [5]. These finding might be due to use of relatively inactive chemotherapeutic drugs in some studies , the lack of sufficient dose intensity or insufficient length of treatment (e.g. 1 to 2 cycles compared to 3 cycles) resulting in an unacceptably low CR rates. Some of these studies also had insufficient no of patients to achieve statistical significance and in some radiotherapy doses & schedules were sub-optimal[5]. Data on NACT prior to surgery is encouraging. Mainly patients with stage IB-IIA disease have been included in these studies. Response rate have ranged from 75% to 100% with clinical CR rates ranging from 11% to 44%. The operability rate ranged from 33 to 100% (cumulative rate 70%) of treated patients. An interesting observation is the reduced incidence of positive lymph nodes after neoadjuvant chemotherapy (6 % to 23%).[6]

The National Cancer Institute (USA) issued an alert in February 1999 that concomitant chemo-radiotherapy should be considered for all patients with cervical cancer, based on evidence from five randomized controlled trials.[7] Subsequently, many other randomized trials have been reported comparing concomitant chemo-radiotherapy versus radiotherapy alone. In addition, meta analysis and systemic reviews on these trials and practice guidelines have also been published. Green et al for Cochrane systemic database review have recently updated the data on 4921 patients enrolled in 24 randomized trials (21 published and 3 unpublished). The review strongly suggests chemoradiation

improves overall survival (10%) and progression free survival (13%), with both platinum and non platinum chemotherapy. There was, however, statistical heterogeneity for these outcomes. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients. Chemoradiation also showed significantly decreased risk of local recurrence and a suggestion of reduction in distant recurrence. Acute haematological and gastrointestinal toxicity was significantly greater in the concomitant chemoradiation group. Late effects of treatment were not well reported and so the impact of chemoradiation on these effects could not be determined adequately. Treatment-related deaths were rare.[8]

So how does concomitant chemoradiation work? In addition to reduction in tumour size, and eradication of micro-metastasis, chemotherapy interact synergistically with RT. Cell cycle synchronization, inhibition of repair of sub-lethal damage or inhibition of recovery from potential lethal radiation damage and hypoxic cell sensitization are some of the possible mechanisms of chemotherapy-radiotherapy interaction.

The choice of chemotherapy (cisplatin alone vs cisplatin + 5 – fluorouracil (5FU) or similar combination) and optimum schedule is unclear at present. Weekly cisplatin 40 mg/m2 concurrent with radiotherapy is well tolerated. Protracted venous infusion of 5-FU did not show superior outcome over weekly cisplatin in a recent study. Direct comparison between cisplatin and cisplatin + 5FU would be of interest. The dose and fractionation of radiotherapy also need to be optimized in future studies.[9]

Thus, present evidence indicate that patients of cervical cancer with stage IB, IIA and II B disease with poor prognostic features (4 cm or bigger and /or pelvic lymph node involvement) and those with distal stage II B, III and IVA should be considered for treatment with concomitant chemo-radiotherapy. For patients with stage IB1, IIA, and proximal IIB stages with good prognostic features (under 4 cm and without pelvic lymph node involvement (radiology or after surgery) and without microscopic invasion of parametrium,if operated standard radiotherapy or surgery remains the standard treatment (presently there is no evidence of benefit of chemotherapy in this subgroup).

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