CRP E33026

Clinical/Radiobiological Study on Viral-Induced Cancers' Response to Radiotherapy, with Comprehensive Morbidity Assessment

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Summary:

Cervix cancer is one of the more common malignancies in women, particularly in developing countries. A vast majority of the cases are diagnosed in locally advanced stages of the disease, but cure with radiation still is possible.

Radiotherapy plays a dominant role in the treatment of cancer of the uterine cervix. Its curative potential depends greatly on the management of intracavitary brachytherapy (BT), which is administered in combination with external irradiation (EBRT). BT can be either of low dose rate (LDR) or increasingly there is use of high dose rate (HDR). HDR BT is traditionally given in 3 to 6 fractions. However, the use of a 2 fraction regime would double the available physical and human resources. It would also help to shorten the treatment and hence reduce hospital visits for patients.

Since local control still remains a problem in patients with advanced cervical cancer, there have been several trials testing chemotherapy with radiation therapy. There appears to be mixed results with cisplatin and radiation, but cisplatin is increasingly used internationally. Since cisplatin requires increased resources of personnel and money, and can result in increased toxicity, testing the drug with radiation is important.

The association of levels of particular molecular markers with radiotherapy outcome may enable different doses to be delivered to individual patients, producing an overall increase in tumour control without increasing morbidity.

Cancer is a growing public health problem in developing countries. Due to lack of public education and scarcity of adequate health care facilities most patients present with advanced disease. In these patients, radiotherapy plays an indispensable role in both curative and palliative treatments. During radiotherapy, various adverse events occur as a consequence of irradiation of normal tissues.

The ARBR Section plans to add a component on improvement of the capture and assessment of long-term normal tissue effects of radiotherapy, to test the use of specially designed questionnaires that could improve adverse event reporting through the use of electronic capture mode. Questionnaires will be used face to face for patients enrolled and the data obtained that way would be compared with data obtained using the traditional way from patient notes.

Overall Objective:

- (remaining part of E3.30.24): The overall objective of CRP (E3.3024) was to test the clinical outcome and toxicity of a resource-sparing schedule of radiotherapy with or without chemotherapy treatment for cervix cancer, to detect molecular markers that will predict tumor control/resistance and to establish whether E6 and E7 viral proteins predict cellular radiosensitivity in oxic and hypoxic conditions in vitro and tumor control/resistance in vivo.
- (new component): The overall objective of the new component of the CRP is to optimize the data capture, provide more details of normal tissue outcomes following

cancer treatments in developing countries and validate this approach using patients participating in the ongoing CRP (E3.30.24). This objective will be achieved by exploring data capture using the questionnaire template on a computer in face-to-face interviews ("active" data collection) and comparing it with standard data collection obtained from the clinical notes ("passive" data collection) during a still-ongoing (old) CRP E3.30.24. The method of data collection will be chosen at random for each case stratified by centre. The ideas for this new CRP component were initially discussed during the Technical Meeting held in Atlanta, October 2004 (TM27167) and then formalized during a consultants meeting held in Denver in October 2005 (05CT09248). The reason for using an ongoing CRP is that it will test the usefulness of the new method and validate it in a multicentre study. While this new aspect falls under another programme task (F3.04/5), different from the objectives (F303/7) of the ongoing CRP (E3.30.24), it is envisaged to combine the remainder of the ongoing CRP with a new component in order to address the new objectives in a newly created CRP. During the performance of the new CRP, the same institutions as for E3.30.24 will be engaged.

Specific Research Objectives:

- Specific research objectives of the remaining part of CRP (E3.3024) (L&H trial) were
    - To compare locoregional control, survival, acute and late effects of two vs. four HDR brachytherapy fractions to treat patients with Stages IIB and IIIB Cervix Cancer
    - To determine if cisplatinum when given concurrently during the external beam radiation phase of treatment leads to additional tumor control or toxicity
    - To explore patterns of protein expressions in tumour cells suitable antibodies to a range of proteins in tumour sections, and to assess any associations of these patterns with tumor control
    - To measure the radiosensitivity of cervix cancer cell lines in oxic and hypoxic conditions, using cell lines infected with these characteristic cervical viral oncoproteins; and if possible, to use the E6 and E7 markers in tissue samples from the patients in this study, to assess any associations with tumor control or resistance to treatments.
- Specific research objectives of the new component are:
    - Can a questionnaire (Annex 2) approach be used effectively in a multicenter, multinational study?
    - Do CTCAE questionnaires improve the collection of normal tissue toxicity data compared to use of toxicity tables?
    - Does data capture using the electronic version of the questionnaire at the point of care facilitate and improve the efficiency of data collection?
    - Is electronic questionnaire ("active") data capture seen as an advantage for the late assessment of the therapeutic benefit over conventional ("passive") data acquisition?

Expected Research Outputs:

- It is expected that the existing CRP component will demonstrate that two fractions of HDR brachytherapy are equivalent to 4 fractions of HDR, with or without chemotherapy in locally advanced cervix cancer (L&H trial).
- It is expected that the new component will demonstrate that use of the questionnaire approach will be feasible in a multicenter, multinational study and that the data collected in this way will compare favourably with conventional means of case note review i.e. will be more complete and will involve greater detail. The data will answer the question as to whether data capture using the questionnaire template on a computer improves the efficiency and ease of data collection i.e. the time taken to record information for active and passive methods and could be applied to further clinical studies if it proves to be of benefit.

Participating institutions:

1. AUSTRIA: University of Vienna; Department of Radiotherapy and Radiobiology; Vienna (QA brachytherapy).
2. BRASIL: Irmandade de Santa Casa de Misericordia de Porto Alegre; Hospital Santa Rita; Porto Alegre.
3. CANADA: Peel Regional Cancer Centre; Mississauga, Ontario (data management).
4. INDIA: Department of Atomic Energy (DAE); Tata Memorial Centre (TMC); Tata Memorial Centre; Mumbai.
5. T.F.Y.R. of MACEDONIA: Radiotherapy and Oncology University Clinic; Skopje.
6. MOROCCO: Institut National d'Oncologie; Rabat.
7. PAKISTAN: Bahawalpur Institute of Nuclear Medicine and Oncology (BINO); Bahawalpur.
8. PERU: Instituto Nacional de Enfermedades Neoplásicas; Lima.
9. R. of KOREA: National Cancer Center; Seoul.
10. SOUTH AFRICA: University of Cape Town; Groote Schuur Hospital; Department of Radiation Oncology; Cape Town
11. UK: Christie Hospital; NHS Trust; Manchester (data management morbidity study).