Best Practice & Research Clinical Gastroenterology 30 (2016) 641–653

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

11

Anal cancer – What is the optimum chemoradiotherapy?

A. Vinayan, MB, BS, MRCP, FRCR,
R. Glynne-Jones, MB, BS, FRCP, FRCR *

Mount Vernon Centre for Cancer Treatment, Northwood, Middlesex HA6 2RN, UK

Keywords:
Squamous cell carcinoma of the anus
Anal carcinoma
Chemotherapy
Immunotherapy
Irradiation
Radiotherapy
Chemoradiation
Combined modality local recurrence

A B S T R A C T

Radical concurrent chemoradiotherapy with 5FU and Mitomycin C is the standard-of-care for squamous-cell carcinoma of the anus (SCCA). Phase III trials combined radiation doses of 50–60 Gy with concurrent Fluoropyrimidines, Mitomycin C and Cisplatin in various doses and schedules. CRT is highly successful for early T1/T2 cancers, but results in appreciable late morbidities and still fails to control larger and node-positive tumours.

Compliance to chemotherapy is important for local control. Modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), rotational IMRT, image-guided radiotherapy (IGRT) have enabled smaller margins and highly conformal plans, resulting in decreased radiation doses to the organs at risk and ensuring a shorter overall treatment time. These advances offer the potential for integrating higher doses of radiation, escalation of the currently used drugs and the safe use of other more novel agents with acceptable toxicity. In this chapter potential novel approaches are discussed in the context of SCCA.

Introduction

Squamous cell carcinoma of the anus (SCCA) is uncommon and represents approximately 2% of all the gastrointestinal malignancies [1]. Following the pioneering study of Nigro in the 1970's [2],

* Corresponding author. Tel.: +44 (0)203 826 2434.
E-mail addresses: anupvinayan@nhs.net (A. Vinayan), Rob.glynnejones@nhs.net (R. Glynne-Jones).

http://dx.doi.org/10.1016/j.bpg.2016.06.005
1521-6918/

several confirmatory studies [3–7] and a series of randomized trials [8–13] all confirmed concurrent chemo-radiation (CRT) with Mitomycin-C (MMC) and 5 Fluorouracil (5FU) as the standard of care both in Europe and North America for locally advanced SCCA.

This schedule results in complete tumour regression in 80–90% of cases overall with a high level of permanent disease control particularly for cT1/T2 tumours. Preservation of relatively normal sphincter function is achieved in the majority of cases, but there is a considerable risk of faecal incontinence [14]. However, more advanced T3/T4 cancers with nodal metastases are more difficult to control [13,15].

Radiation alone can result in local control of disease in approximately 45–56% even in locally advanced SCCA [9,10]. To increase the effect of radiation, chemotherapeutic agents can be administered before radiotherapy (neo-adjuvant or induction), concurrently with radiotherapy or after radiotherapy (consolidation or maintenance). However, in clinical studies, only concurrent chemoradiation has been shown to improve disease-free survival and colostomy free-survival.

In general, the anticancer drugs that have proved to be most effective with radiation are 5-fluorouracil, mitomycin C, cisplatin and the taxanes either alone or in combination. Cisplatin interacts with nucleophilic sites on DNA or RNA to form intra-and inter-strand crosslinks [16] and also inhibits cellular repair processes. Chemotherapy can also stall cells in the radiosensitive phases of the cell cycle (G2 and M phases) or eliminate cells in the radio-resistant phase (S-phase). However, concurrent chemotherapy also enhances radiation damage to normal tissues, and potentially causes severe acute and late toxicity [17].

The European historical standard of care relied on split-course radiotherapy with high total doses and interstitial implants [9,10] based on the tradition of Papillon. A planned gap between the completion of CRT and a boost allowed the acute toxicity of skin and mucosal surfaces to resolve, the tumour to shrink and permitted an interstitial implant to the smallest possible volume. This practice minimised the risk of necrosis in the high dose area. Another rationale for the gap was to select patients who fail to respond for salvage either by dose-escalation or by surgical resection as salvage.

The ACT II trial utilised low total doses of 50.4 Gy with multiple phases, and mandated an uninterrupted radiation strategy. Intensity-modulated radiotherapy (IMRT) or rotational IMRT with simultaneous integrated boost (SIB), image-guided radiotherapy (IGRT) using cone-beam CT (CBCT), and stereotactic techniques have produced highly conformal plans, which potentially allow dose escalation to primary macroscopic tumour and retreatment of small nodal recurrences. IMRT has decreased average and threshold doses to the organs at risk (OARs), such as the male and female genitals, perineum, bladder, hip, and small bowel, compared with conventional 3D-Conformal RT [18] IMRT also appears successful in maintaining dose without extending overall treatment time (OTT).

Around 80%–90% of SCCA is associated with HPV infection with the majority linked with HPV-16 and HPV-18 HPV contributes to progression of SCC via the action of the HPV onco-proteins E6 and E7, which interact with tumour suppressor proteins such as p53 and pRB to disrupt the cell cycle and maintain a transformed phenotype. HPV positivity and p16 positivity is considered a positive prognostic factor with better response to the CRT and improved oncological outcomes.

The oncogenic potential of these viruses is thought to be partly due to viral protein E6 and E7, which modulates the cell cycle checkpoint resulting in uncontrolled cell division. Significant interest is gaining ground in using immunotherapy with cell cycle checkpoint inhibitors and inhibitory molecules, such as programmed death receptor −1 (PD-1) and its ligands, PD-L1 and PD-L2.

In this review, we discuss the current evidence basis for the approved treatment regimens and look into the novel approaches and therapies that are being developed for SCCA.

Methods

A computerized literature search examined relevant English language literature using Medline and Cancerlit (1985 to December 2015 inclusive), supplemented by hand searching of abstracts from the proceedings of the American Society of Clinical Oncology and other international meetings since 2000. The search strategy employed the key words – local recurrence, chemotherapy, immunotherapy, synchronous, concurrent, irradiation, radiotherapy, chemoradiation, radiochemotherapy,