Digestive and Liver Disease 49 (2017) 1262–1266

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Early closure of fistula using neo-adjuvant intra-arterial chemotherapy in locally advanced anal cancer

Wulfran Cacheux[a,*,1], Thibaud Koessler[a,1], Giacomo Puppa[b], Eugenio Fernandez[a], Lisa Ho[b], Pierre-Yves Dietrich[a], Thomas Zilli[c], Abdelkarim Said Allal[d], Bruno Roche[e], Frederic Ris[e], Arnaud Roth[a]

[a] Department of Oncology, University Hospital of Geneva, Geneva, Switzerland
[b] Department of Pathology, University Hospital of Geneva, Geneva, Switzerland
[c] Department of Radiation-oncology, University Hospital of Geneva, Geneva, Switzerland
[d] Department of Radiation-oncology, University Hospital of Fribourg, Fribourg, Switzerland
[e] Department of Surgery, Clinic for Visceral and Transplantation Surgery, University Hospital of Geneva, Geneva Switzerland

ARTICLE INFO

Article history:
Received 1 April 2017
Received in revised form 29 August 2017
Accepted 29 August 2017
Available online 5 September 2017

Keywords:
Anal cancer
Chemotherapy
Fistula
Intra-arterial

ABSTRACT

Background: Locally advanced anal cancer patients, especially with T4 disease and fistula, have a dismal prognosis. Neo-adjuvant intra-arterial chemotherapy before standard chemoradiation has been shown to be promising in this setting.
Aims: We are reporting results from a larger patient population.
Methods: From 2005 to 2015, 25 consecutive patients with locally advanced anal cancer, 18 of them fistulised, received intra-arterial chemotherapy.
Results: Twenty-two of 25 patients (88%) had T4N0-3 disease and 3 (12%) T3N3. An objective tumour response was observed in 24 of 25 patients (96%): 24 partial responses and 1 with stable disease. Fistulas' complete closure was observed in 15 of 18 patients (83.3%). Following intra-arterial chemotherapy, 23 patients underwent chemoradiation. Twenty-one of 25 patients (84%) had a complete remission 6 months after treatment completion. Amongst 22 patients followed for 3 or more years, 18 of them (81%) are colostomy free at 3 years. Five-year overall survival is 75%. Most frequent grade 3–4 toxicity of IAC was neutropenia (25%).
Conclusions: Neo-adjuvant intra-arterial chemotherapy combined to chemoradiation resulted in a high rate of fistulas closure and long-term control of locally advanced anal cancer. This interesting approach in the treatment of fistulised anal cancer, needs a prospective study before being considered a new standard strategy.

1. Introduction

Anal squamous cell carcinoma of the anus (ASCC) remains a rare disease despite an increasing frequency in the population, with an annual incidence of 1,5 cases per 100,000 people per year worldwide [1,2]. ASCC is highly sensitive to chemoradiation (CRT). CRT increases local control, colostomy-free rates and overall survival rates compared with radiotherapy (RT) alone [3–5]. CRT with concurrent 5-fluorouracil and mitomycin C-based chemotherapy represents the current standard of care, with 3-year and 5-year disease-free survival rates of about 73% and 68% respectively [6,7]. Abdomino-perineal amputation (APA) is usually reserved for patients who present a local relapse after CRT [8]. T stage is known to be an independent and major prognostic factor in several prospective studies [9–11]. Anal tumours that invade adjacent organs, as the vagina and the urinary tract, are staged T4. T4 tumours have a correspondingly poor prognosis after CRT with approximately a 5-years overall survival rate of less than 45% and a five-year disease-free survival rate of less than 35% [12,13]. Anal cancer-related fistulas are also known to be debilitating complications in the course of the disease but no specific data of 5-years overall survival and 5-year disease-free survival rates are available. In general, patients with T4 and/or with fistulas are treated with a diverting stoma followed by standard CRT. There is a theoretical

* Corresponding author at: Department of Oncology, University Hospital of Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland.
E-mail address: wulfran.cacheux@curie.fr (W. Cacheux).
[1] These authors contributed equally to this work and serve as co-first authors.

http://dx.doi.org/10.1016/j.dld.2017.08.039
1590-8658/

concern that radiation therapy might enlarge fistulas and render any surgical attempt to close them hazardous. Furthermore, the rate of stoma reversal in this group of patients is unsurprisingly low [14]. Hence, there is room for an effective conservative approach to close fistulas before standard CRT. To our knowledge, there is no clear published evidence to guide the management of initial T4 stage tumours with anal cancer-related fistulas. Our group has previously reported activity of intra-arterial chemotherapy (IAC) in locally advanced ASCC and a series of 8 cases of 4 complete closure of cancer-related ano-vaginal and ano-perineal fistulas with IAC followed by combined CRT [15,16]. We hereby report an updated series of 25 chemo-naive patients with exclusively locally advanced ASCC and/or ASCC-related fistulas undergoing IAC followed by standard therapy.

2. Materials and methods

2.1. Patients selection

We retrospectively reviewed all the patients with ASCC from 2005 to 2015 in our institution. Only naive patients receiving IAC before CRT were included. Consecutive patients with very advanced and symptomatic disease or those with fistulas to organs or to skin were recruited. None of the patient were metastatic at the time of the diagnosis. Detailed physical examination and imaging exams (CT scan, pelvic MRI and/or anorectal echo-endoscopy) were used to assess the tumour staging. Fistulas were detected and assessed before IAC during the clinical examination and the pelvic MRI study. Patients with performance status over 2 and age over 80 were excluded. All the patients were scheduled to receive 4 cycles at the maximum, however treatment was interrupted earlier as soon as the fistula was closed or in case of treatment intolerance whichever came first. This retrospective study was reviewed and approved by the Ethics Committee of the University Hospital of Geneva (No. 14-234).

2.2. Intra-arterial chemotherapy regimens and protocol

As described previously, the patients received neo-adjuvant IAC through a 4 to 5F pigtail catheter inserted by femoral catheterization into the aorta, distally from the inferior mesenteric artery [15]. IAC was given every 6 h on 2 consecutive days and consisted of rapid push injections of the 4 following drugs: 5-fluorouracil 275 mg/m^2, methotrexate 27.5 mg/m^2, mitomycin C 1.2 mg/m^2 and cisplatin 8.5 mg/m^2 or oxaliplatin. Furthermore, we administered bleomycin at a total dose of 10 mg intravenously on days 1, 8, and 15. Folinic acid rescue was started on day 1 and consisted of 15-mg tablets given every 6 h for 6 days. Pegfilgrastim was injected subcutaneously at a dose of 6 mg on day 3. The whole procedure was repeated at intervals of 5 weeks. Neo-adjuvant IAC was followed by standard CRT to 59.4–60 Gy with 2 cycles of concomitant mitomycin C and 5-fluorouracil.

2.3. DNA extraction and HPV genotyping

5–10 sections of 10 μm from each sample were used to extract DNA following the instructions of QIAamp DNA FFPE tissue kit (QiagenGmbH, Germany). 100 ng genomic DNA was used to perform polymerase chain reactions (PCR) using PGMY primers or modified general primers GP5+/GP6+ (MGP) [17]. HPV (Human Papilloma Virus) genotype was identified using the Linear Array® HPV Genotyping Test (Roche Molecular Diagnostics). The test allows the detection of 16 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82) and 21 low-risk types (6,11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, IS39 and CP6108). For cases which were negative for HPV, betaglobin of 400 bp was amplified by PCR to test the integrity of DNA extracted.

2.4. Assessment of chemotherapy response

Tumour responses were assessed by visual inspection at each visit and by using Response Evaluation Criteria in Solid Tumours (RECIST) criteria [18]. Disappearance of primary lesion without lymphadenopathy >1.0 cm was considered complete response (CR). Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of target lesions with or without residual lymphadenopathy >1.0 cm. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of target lesions. Tumour response that did not meet these criteria was defined as stable disease (SD). Fistulas were detected and assessed before IAC during the clinical examination and the pelvic MRI study. The IAC-related toxicity was graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

2.5. Statistical analysis

Categorical values were analysed using a chi-square test with Yates correction when the frequency is less than 5 in more than 20% of our conditions. Colostomy-free survival (CFS) was measured from the date of diagnosis until the date a colostomy was done; CFS at 3 year was the primary outcome of the study. Relapse-free survival (RFS) is the time between the last day of RT and the date at which a relapse is diagnosed overall survival (OS) was measured from the date of first cycle of IAC until death as a result of any cause. The Kaplan-Meier estimate was used to estimate OS with STATA version 8 (Stata Corporation, TX, USA).

3. Results

3.1. Patient and tumour characteristics

A total of 25 consecutive patients with histopathological proven ASCC undergoing IAC were included in this study. There were 20 females and 5 males. The median age at the diagnosis was 56,5 years (ranging from 33 to 79 years). Only one patient had HIV infection. Twenty-two of 25 patients (88%) had T4N0-3 tumours and 3 of 25 patients (12%) had T3N3 tumours (AJCC-2010) with large symptomatic inguinal node involvement (compressing vascular axis or with skin fistula). Most patients (84%) had stage IIIB (T3N3, T4N1, T4N3) disease and 16% stage IIIA (T4N0). Twenty-one of 25 patients (84%) had N+ tumour. Eighteen of 25 patients (72%) had symptomatic fistulas. More than 80% of the patients (18/22) had an adjacent organ invasion in 50% of the case this fistula was to the vagina. Tumoral diameter was <5 cm in 9 patients and ≥5 cm in 16 patients. An initial colostomy was performed in 7 of 25 patients (28%). HPV status was determined in 22 tumours for the other 3 no tissue was available. Out of 22 HPV positive patients 20 were affected with HPV 16. Patients and tumour chracteristics are summarized in Table 1.

3.2. IAC and tumour response

A total of 61 cycles of IAC were administered in 25 ASCC patients. The number of cycles of IAC was adapted according to tumour response and tolerance (range, 1–4 cycles), 96% of the patients received 2 or more cycles (3 cycles in 4 patients (16%) and 4 cycles in 4 patients (16%)). One patient discontinued IAC after 1 cycle due to haematological toxicity (grade 4 thrombopenia). No complete response was observed, 24 of 25 patients (96%) had a partial