20 Applications to Gynecological Cancers

Anthony W. Fyles, Michael Milosevic, and Amit Oza

CONTENTS

20.1 Introduction

Since the publication of five randomized trials of platinum-containing chemo-radiation in women with cervical cancer in 1999, and the accompanying National Cancer Institute (NCI) Clinical Announcement, combined treatment has become the standard of care in this disease (Rose et al. 1999; Whitney et al. 1999; Morris et al. 1999; Keys et al. 1999; Peters et al. 2000). In women with vulvar cancer, trials of chemo-radiation for locally advanced tumors have shown good response rates, consistent with their similar histology and etiology to cervix tumors. Despite this, local and distant relapse continue to be significant problems, particularly for patients with bulky tumors; hence, the interest in improving combined modality treatment, ideally without further increasing toxicity.

Current areas of interest in gynecological cancers include combinations of novel agents and standard chemo-radiation, including cytotoxics and biologically targeted agents. These targets may be microenvironmental (e.g., tumor hypoxia and interstitial hypertension; angiogenesis), growth factors such as epidermal growth factor (EGF), or, for example, can be directed against epigenetic events such as DNA methylation.

In this chapter we review current and upcoming trials investigating new chemo-radiation protocols for women with gynecological cancers, focusing specifically on cervix and vulvar cancer, where combined treatment is most frequently used. We begin by discussing prospective studies of cytotoxic agents in combination with radiation, followed by a review of hypoxia-targeted agents, and finish with an update of current and proposed studies of biologically targeted agents in combination with radiation and chemo-radiation.

20.2 Chemo-Radiation Using Cytotoxic Agents in Cervical Cancer

20.2.1 Randomized Clinical Trials

A recent meta-analysis of randomized chemo-radiation trials in cervical cancer demonstrated a 10% absolute survival improvement, largely due to improved pelvic control, but with a suggestion of improved distant relapse (Fig. 20.1; Green et al. 2005). Most of these trials used concurrent cisplatin-containing chemotherapy although benefit was also

A. Fyles, MD; M. Milosevic, MD
Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, Toronto, ON M5G 2M9, Canada
A. Oza, MD
Department of Medical Oncology and Haematology, Princess Margaret Hospital, 610 University Avenue, Toronto, ON M5G 2M9, Canada

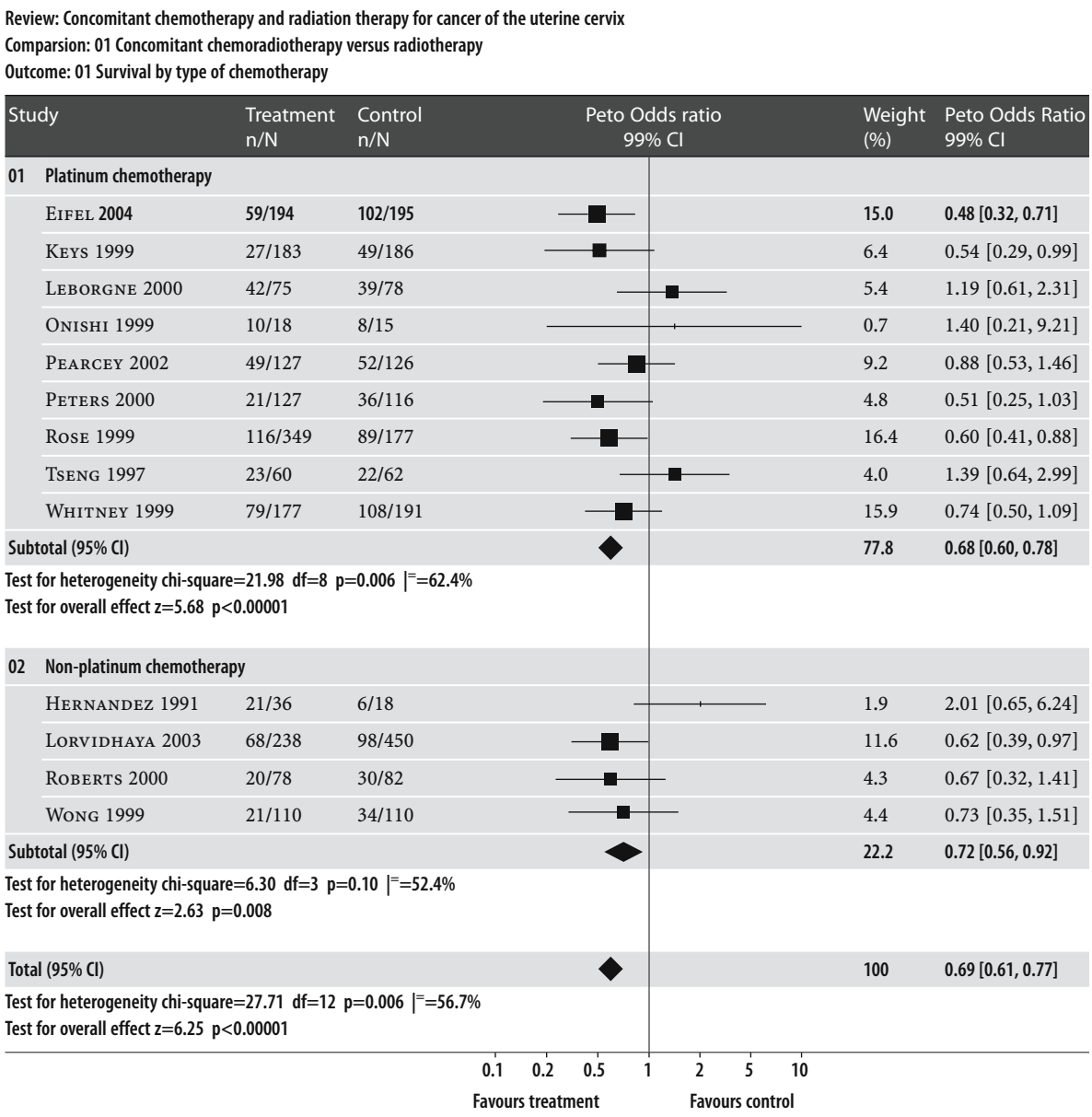

Fig. 20.1. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix

seen in studies of other agents such as mitomycin C and 5-fluorouracil (5-FU). Not included in the meta-analysis was a recent randomized study comparing infusional 5-FU vs cisplatin that was stopped early due to an increased risk of relapse in the 5-FU arm (Lanciano et al. 2005; note that there have been no direct comparisons of different cisplatin regimens such as cisplatin alone vs cisplatin and 5-FU).

The benefit of chemo-radiation was at an increased cost in acute toxicity, particularly hematological, as well as nausea and vomiting, which are usually manageable with suitable supportive care. Weekly cisplatin is felt to be associated with lesser toxicity than cisplatin/5FU [particularly gastrointestinal (GI)] and appears to be the favored regimen (Lukka and Johnston 2004). There was uncertainty about the risk of increased late toxicity (Maduro et al. 2003) and a patient-based meta-analysis is underway for an upcoming Cochrane review.

These results would suggest that the current policy of cisplatin alone on a weekly basis, or with 5-FU given every 3 weeks, is reasonable and associated with significant benefits and manageable toxicity; however, despite these improvements, patients