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Introduction to managing patients with recurrent ovarian cancer

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ABSTRACT

Ovarian cancer is the 5th most common cancer found in women in the UK. It is the leading cause of death from gynaecological cancer, and is the 4th most common cause of cancer death among UK women. Similar to the majority of other cancers, relative survival rates for ovarian cancer are improving, although 5-year mortality rates remain stubbornly low. The stage of the disease at diagnosis is the single most important determinant of ovarian cancer survival, as many patients first present with advanced disease. Treatment of ovarian cancer involves a combination of 'upfront' primary surgery followed by chemotherapy. Platinum/taxane-based chemotherapy is the recommended standard-of-care first-line chemotherapy, but the majority of patients will relapse with drug-resistant disease within 3-5 years. However, not all patients can continue with platinum combination therapies due to loss of activity or toxicity-related issues, including hypersensitivity, neurotoxicity, alopecia and ototoxicity. Therefore the choice of second-line chemotherapy must take into account factors such as platinum-free treatment interval (PFI); patient's performance status; current symptoms; history of and likely future toxicities while on chemotherapy; dosing schedule requirement; and cost of treatment. A consensus in 2010 established 4 distinct subgroups within the ROC patient population based on the PFI: (platinum sensitive >12 months, partially platinum sensitive 6-12 months, platinum resistant <6 months, and refractory disease ≤4 weeks). Within patients with platinum sensitive disease, those with partially platinum sensitive disease remain the most clinically challenging to manage effectively. Non-platinum based combination therapies, in particular trabectedin with pegylated liposomal doxorubicin (PLD), offers new options together with a significant survival advantage relative to PLD alone for these patients.

Prevalence of ovarian cancer and recurrent ovarian cancer in the UK

Ovarian cancer is the fifth most common cancer among women in the UK (2011), accounting for 4% of all new cases of cancer in females. Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older women; age-specific incidence rates rise sharply from around age 35-39, peak in those aged 80-84, and subsequently plateau (Fig. 1). However there has been a decrease of 11% in overall incidence over time, probably because of the contraceptive pill that is known to reduce the risk of ovarian cancer [1].

Mortality rates due to ovarian cancer in the UK are significant. Ovarian cancer is the leading cause of death from gynaecological malignancies and is the fourth most

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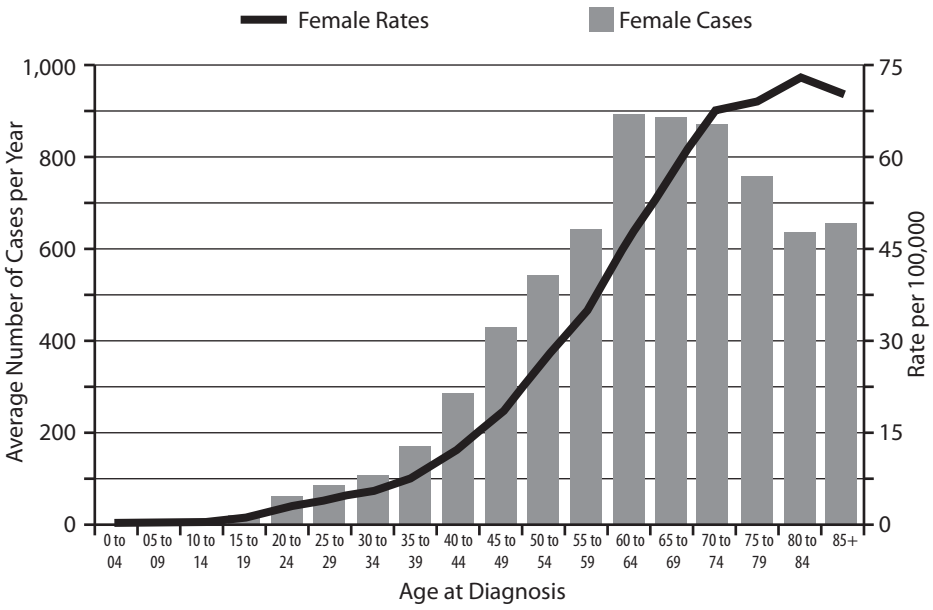

Fig. 1 – Ovarian cancer: average age of new cases per year and age-specific incidence rates per 100,000 population, females, UK (2009-2011).

common cause of cancer death among females in the UK (2011), accounting for 6% of all female deaths from cancer. This amounts to 13 ovarian cancer deaths for every 100,000 females in the UK, with the highest mortality rates being in older women (>65 years) [1,2].

However, as with the majority of cancers, relative survival for ovarian cancer is improving. The latest age-standardised relative survival rates for ovarian cancer in the UK during 2005-2009 show that 72.3% of women are expected to survive their disease for at least one year; with this figure falling to 42.9% surviving five years or more. The relatively low five-year survival rates can be attributed partly to the fact that 29% of cases of ovarian cancer are emergency presentations due to the non specificity of symptoms. For example, data from the Anglia Cancer Network area for women diagnosed during 2004-08 show that five-year relative survival rates are more than 90% for early stage disease, but fall very sharply to less than 10% for late stage cases [1]. Demonstrating the importance of the stage of the disease at diagnosis as a determinant of ovarian cancer survival.

Nevertheless, five-year relative survival rates for ovarian cancer increased from 21% in England and Wales during 1971-1975 to 42.9% in England during 2005-2009 (Fig. 2). It is thought that the significant increase in one-year survival is likely to be the result of greater use of platinum-based chemotherapy regimens. And the increase in five-year survival may be due to both wider access to optimal primary treatment and a greater determination by the clinical community to treat recurrent disease [3].

When UK survival rates for ovarian cancer are compared with those of other high income countries, including in Europe, they are significantly worse. Incidence and mortality rates due to ovarian cancer in the UK are on a par with Eastern Europe and higher than those given for Germany, France and Italy. Differences in data quality and coding practices may contribute to some of the variation, but the consistently lower levels for the UK suggests real differences in survival, which demand further investigation and earlier access to specialist care and improved treatment options for UK patients [4,5].

Management of patients with ovarian cancer

Treatment of ovarian cancer involves a combination of surgery and chemotherapy. 'Upfront' primary surgery for complete resection if possible or cytoreductive surgical debulking for advanced disease, followed by chemotherapy remains the international standard of care. Chemotherapy, however, has been principally responsible for the improved survival seen over the past 10 years [3,6].

As previously described platinum combination (typically platinum-paclitaxel) chemotherapy has been established as the standard of care following surgery for ovarian cancer [7].

Management of patients with recurrent ovarian cancer

For relapsing patients with recurrent disease, relatively few phase III studies have been conducted and these have been primarily in patients with platinum-sensitive (PS) disease. The International Collaborative Ovarian Neoplasm 4 (ICON-4) trial was the first to show that a combination of platinum and paclitaxel was more effective than single-agent platinum compounds in patients with relapsing PS ovarian cancer. The carboplatin/paclitaxel combination increased PFS by a median of 3 months (12.0 vs. 9.0 months; p=0.0004) and OS by 5 months (29.0 vs. 24.0 months; p=0.02) when compared with carboplatin alone. [8] By comparison, the Intergroup study by Pfisterer et al. showed that a gemcitabine/carboplatin combination was associated with a median improvement in PFS of 2.8 months (8.6 vs. 5.8 months; p=0.0031) in patients with PS disease, but with greater toxicity and no improvement in OS (18.0 vs. 17.3 months) and QoL compared with carboplatin alone [9]. And, the large phase III CALYPSO trial showed that