Game Changers

ORAL DRUG THERAPY – IMPROVING SURVIVAL IN MALIGNANT MELANOMA

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The incidence of melanoma continues to increase. In early-stage disease, 5-year survival rates with surgical resection exceed 90%, however, stage III and IV disease has a higher risk of recurrence after resection, and many will ultimately die from metastatic melanoma. Since 2012 there has been a rapid increase in NICE approved therapy for patients with metastatic melanoma, with long-term survival now a reality for selected patient groups.

Novel oral agents targeting the MAP kinase pathway, specifically oncogenic mutations in BRAF (present in approximately 40% of melanomas), have enhanced outcomes.[1,2] Treatment with the BRAF inhibitor, dabrafenib, plus the mitogen-activated protein kinase kinase (MEK) inhibitor, trametinib, result in clinical benefit in over 90% of patients treated (median survival now approaching 3 years). This combination is routine practice in Northern Ireland, allowing treatment of severely unwell and symptomatic patients who previously may not have been suitable for chemotherapy, with often rapid resolution of symptoms within days to weeks.

Furthermore, this therapy has shown response rates in excess of 50% in patients with symptomatic brain metastases, improving symptoms and quality of life, providing options where once there were few and has largely superseded whole brain radiotherapy in this setting.[3]

More recently, the adjuvant COMBI-AD trial[4] reported that patients with completely resected BRAF mutation melanoma treated with dabrafenib/trametinib for one year had improvement in the rate of relapse-free survival at 3 years of 58% vs. 39% with placebo, as well as improvement in survival at 3 years of 86% vs 77% . BRAF/MEK inhibitors in the adjuvant setting are expected to enter routine clinical practice following regulatory approvals.

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2. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *New England Journal of Medicine*. 2015;**372(1)**:30-39.
3. Davies M, Saiag P, Robert C, Grob J, Flaherty K, Arance A et al. Dabrafenib plus trametinib in patients with BRAF V600 -mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *The Lancet Oncology*. 2017;**18(7)**:863-873.
4. Long G, Hauschild A, Santinami M, Atkinson V, Mandalà M, Chiarion-Sileni V et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *New England Journal of Medicine*. 2017;**377(19)**:1813-1823.

RADIOFREQUENCY ABLATION AND ENDOSCOPIC MUCOSAL IN TREATMENT OF EARLY NEOPLASTIC BARRETT'S OESOPHAGUS

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Barrett's Oesophagus (BO) is a precancerous condition, associated with chronic gastro-oesophageal reflux, resulting in a change of normal squamous epithelium of the lower oesophagus to columnar epithelium. In non-dysplastic BO, the cancer conversion rate is 0.9%/year with increasing cancer risk of 9.1%/year with low-grade dysplasia (LGD) and 25.6% risk with high-grade dysplasia (HGD) over a 3 year period.[1]

Within Northern Ireland, endoscopic therapy for early neoplastic changes has offered patients a less invasive treatment option with curative intent in comparison to the conventional surgical intervention. These include radiofrequency ablation (RFA) of dysplastic BO and endoscopic mucosal resection (EMR) for nodular BO as per NICE recommendations.[2]

All cases are carefully selected and discussed through the regional upper GI cancer multidisciplinary meeting prior to onward referral to an advanced endoscopist competent in performing these procedures.

To date, a total of 282 EMR's have been successfully performed on visible oesophageal lesions and a total of 238 RFA on dysplastic BO with curative intent.

These procedures are generally well tolerated with minimal recovery time and same day discharge. They are performed under conscious sedation and have much lower morbidity and mortality in comparison to an oesophagectomy.

The future reduction in oesophageal cancer risk due to the fact BO can be eradicated highlights the importance of this therapeutic endoscopic intervention for the future.

1. Fitzgerald, R.C., et al., British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut, 2013.
2. NICE, Endoscopic radiofrequency ablation for Barrett's oesophagus with lowgrade dysplasia or no dysplasia. http://www.nice.org.uk/guidance/IPG496/chapter/1-Recommendations, 2014.

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