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Original Article

A Population-based Study of Survival Impact of New Targeted and Immune-based Therapies for Metastatic or Unresectable Melanoma

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Abstract

Aims: New targeted drugs and immune therapies reported since 2010 for metastatic or unresectable melanoma (MM) have shown improved survival in randomised trials. We studied the uptake of these new drugs and their impact on population-based survival.
Materials and methods: This was a retrospective, population-based cohort study of all patients treated for MM in Ontario 2007–2015. Provincial administrative sources covering the whole population identified palliative systemic therapy, radiotherapy and metastasis surgery. Temporal trends in utilisation and survival were investigated, as was survival of treatments predefined as 'new drugs' (BRAF or MEK inhibitors, anti-CTLA4 and anti-PD-1 antibodies).
Results: We identified 2793 treated MM patients. First treatment was systemic therapy (46%), radiotherapy (41%) and metastasis surgery (14%). Systemic treatment increased from 53% of patients (2007) to 75% (2015). New drug treatments increased from <6% of known first-line regimens in 2007 to 82% in 2015. One and 2 year overall survival was 28% and 15%, respectively, for all MM 2007–2009, rising to 46% and 35% for 2014–2015 (adjusted hazard ratio 0.56, 95% confidence interval 0.49–0.63, $P < 0.0001$). Survival gains were observed primarily among those cases initially treated with systemic therapy, which became dominated by the use of new drugs over the study period (2 year overall survival 16% 2007–2009 versus 44% 2014–2015; adjusted hazard ratio 0.46, 95% confidence interval 0.38–0.56, $P < 0.0001$).
Conclusions: Utilisation of new targeted drugs and immune therapies for MM has increased considerably in routine practice 2007–2015. Consistent with the results of clinical trials, adoption was associated with substantial increases in survival of patients in the general population.

Keywords: Anti-CTLA4; anti-PD-1; BRAF inhibitor; effectiveness; metastatic melanoma; population-based study

Introduction

Dramatic survival gains have been reported in clinical trials of new systemic agents for metastatic or unresectable melanoma (MM). Before 2010, MM was considered relatively treatment resistant, with a very modest impact of chemotherapy (e.g. dacarbazine) or radiation therapy. Published trials for the anti-CTLA4 monoclonal antibody ipilimumab first appeared in 2010. Pooled data from ipilimumab-treated patients showed a 3 year survival of 22%, with evidence emerging of a plateau on the survival curve after 10 years of follow-up [1–3]. 2011 saw the first published results of treatment with single-agent BRAF inhibitors, targeting BRAF mutations present in 40–50% of patients, with an observed 30% increase in 6 month overall survival compared with dacarbazine for patients with BRAF V600 E/K mutations (hazard ratio 0.37, 95% confidence interval 0.26–0.55, $P < 0.001$) [4]. Concurrent use of BRAF inhibitor with a MEK inhibitor has shown further improved survival outcomes in a randomised trial setting (hazard ratio 0.70, 95% confidence interval 0.55–0.90, $P = 0.005$) [5]. Anti-PD-1 monoclonal antibodies used alone, or in combination with anti-CTLA4 treatment, have also improved response rates and survival, with 2 year outcomes most often more than double historic results with chemotherapy [6–11].

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In general, the survival impact of new cancer drugs in unselected population-based samples has been understudied. To develop a true understanding of the population impact of emerging therapies and the real value of expensive new agents, population-based analysis is required. Until now, reports have had limitations in content, such as outcomes reported for limited time periods or selected population subgroups [12–14]. Interpretation of these is thus limited and requires confirmation in more comprehensive data sets. No study covering a full population of treated MM patients is available, covering the period before and after adoption for all classes of new drugs, including patients treated in clinical trials.

In Ontario, starting in 2012, new targeted drugs and immune-based therapies for MM began to enter routine practice. We set out to describe the population uptake and outcomes of these new drugs for MM among the full population of MM patients treated with palliative intent in Ontario.

Materials and Methods

Study Population

This was a population-based study of melanoma patients treated for MM between 1 January 2007 and 31 December 2015. Ontario has a single-payer universal health system, with a population of 13.6 million. Melanoma diagnoses were identified through the Ontario Cancer Registry (OCR). Cutaneous and non-cutaneous sites were included. MM cases with additional non-melanoma primary cancers were excluded to minimise the risk of misclassifying treatment information. This study was approved by the Queen's University Research Ethics Board.

Data Sources

The OCR is a passive population-based cancer registry, capturing diagnostic and demographic data, with completeness of at least 98% for all incident cancer cases in Ontario [15]. Records of hospitalisation from the Canadian Institute for Health Information provided information about surgical procedures. Systemic therapy use was identified from Ontario Health Insurance Plan physician billing data, provincial records of systemic therapy delivery and treatment records from regional cancer centres. Cancer centre records were also used to identify radiotherapy. All data sets were linked using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences.

Classification of Independent Variables

Survival according to era of first treatment for MM was investigated (2007–2009, 2010–2012, 2013–2015). All intravenous systemic therapy agents, radiotherapy and cancer surgery are provided in Ontario through a single-payer, publicly funded cancer system co-ordinated by Cancer Care Ontario (CCO). Oral drugs are accessed through a variety of different programmes, but are administered through the publicly funded cancer system.

New drugs were classified as regimens with any of the following: anti-PD-1, anti-CTLA4, targeted therapy (e.g. BRAF, MEK inhibitors) or unapproved agents including clinical trial drugs. Old drugs were cytotoxic or, rarely, hormonal agents (e.g. dacarbazine, carboplatin, paclitaxel, temozolomide, tamoxifen). Drug administration in CCO Activity Level Reporting data with non-palliative intent was excluded from MM-defining treatments. Regimens that were not primarily administered with palliative intent were also excluded as MM-defining treatments, as it was observed that a small number of patients were enrolled on adjuvant drug trials for new agents during the study period. For consistency, treatment information was censored at 31 December 2015 beyond which data completeness was variable.

For radiotherapy, cohort eligibility was based on radiotherapy department activity with palliative treatment intent. Canadian Institute for Health Information hospital separation records for the whole province identified cancer surgeries: brain tumour resection, decompressive spinal surgery, lung resection or liver resection.

Before inclusion on the formulary, population access to some agents was available through extended access programmes or compassionate access programmes. Furthermore, some satellite centres administering systemic therapy may not have reported drug treatments directly to CCO. To address both of these issues, and to ensure our data were as complete as possible, provincial reimbursement data from specialist physicians administering systemic therapy were used to identify cases treated with systemic therapy without a named drug regimen. Physician reimbursements for high-dose interferon (HDIFN) were excluded; this was the only funded adjuvant treatment in Ontario during the study period.

Patient characteristics at the time of first treatment and disease characteristics of the melanoma diagnosis were described. Demographic data were obtained from Ministry of Health and Long Term Care administrative data. Socioeconomic status was based on neighbourhood household income quintiles. The rurality of patient residence at the time of first MM treatment was characterised by the 2008 Rurality Index for Ontario [16]. The Elixhauser comorbidity score was used with 5 year lookback with the Canadian Institute for Health Information Discharge Abstract Database and Same Day Surgery data. Diagnostic codes for primary or metastatic cancer were not counted in the score. To provide sufficient lookback for comorbidity status, patients with lapses in their Ontario Health Insurance Plan coverage in the 5 years before the date of first palliative treatment were excluded.

The time from first melanoma diagnosis in OCR to the first MM treatment was measured. Complete information on second and subsequent melanoma primaries was not available for the full study period and so was not used.

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