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The PICO Model for Effective Learning of Holistic and Comprehensive Care in an Atypical Case of Metastatic Melanoma

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Abstract

Aim and background: PICO is evidence-based research model to create a process for framing a research question, locating, assessing, evaluating, and repeating the question as needed. “PICO” are “P” for “Patient/Problem/Presentation/Population”, “I” for “Intervention/Investigation/Inquiry”, “C” for “Comparison/Concern/Control, O for “Outcome/Outlook”. This model has recently been used frequently in evidence-based medical education in framing the initial question. The aim of this article is to demonstrate the effective use of the innovative PICO model in the senior medical students’ clinical placement learning through reflection of clinical cases on an elective exchange program. The literature on the raised case will be reviewed and discussed to maximize the students’ learning with the innovative PICO model.

Innovation and method: The five equal first authors of this article are interns of the First Affiliated Hospital, Sun Yat-Sen University, whom visited Curtin Medical School and its associated hospitals and general practice clinics for four-week’ supervised clinical placements as medical observers. They have been using the PICO model to learn their daily cases for their daily debrief and summary. Their supervisor was the corresponding author and has identified the opportunity to learn about holistic and comprehensive care by using the PICO model via management with an atypical case of metastatic malignant melanoma.

Result: A general practice case of metastatic malignant melanoma to the brain was selected among the many cases debriefed daily during the four-week’ supervised clinical placements. The PICO model was used to raise the different treatment modalities as questions for investigating the relevant literature, comparing the individual treatment or combined modalities and monitoring the outcomes of the treatment modalities.

Conclusion: The innovative PICO model is an excellent medical educational tool for senior medical students’ learning in clinical placement. The literature on the holistic and comprehensive treatment modalities of metastatic malignant melanoma was reviewed by the students to indicate the future research direction in melanoma management, ultimately enhancing the clinical management skills to improve survival rate of metastatic melanoma in both China and Australia.

Introduction

PICO is evidence-based research model to create a process for framing a research question, locating, assessing, evaluating, and repeating as needed. “PICO” are “P” for “Patient/Problem/Presentation/Population”, “I” for “Intervention/Investigation/Inquiry”, “C” for “Comparison/Concern/Control, O for “Outcome/Outlook”. This model has recently been used frequently as part of best evidence medical education in framing the question for gathering and using evidence in medical education [1]. Hart and Harden, based on the best evidence in medical education recommended five steps in gathering and using evidence in medical education including framing the question, developing a search strategy, evaluating the evidence, implementing change and evaluating that change [2]. The PICO model used in this article is an innovation of the five steps that incorporate developing a search strategy, evaluating the evidence, implementing change and evaluating that change into the last two steps of comparison and outcome analysis. The innovative PICO model aims...
to reflect the change of medical educational approach from opinion-based to evidence-based medical education [3]. The aim of this article is to examine the effective use of this model in the senior medical students’ clinical placement learning through reflection of clinical cases on an elective exchange program. The literature on the clinical case will be reviewed to maximize the students’ learning with the use of innovative PICO model. An atypical case of metastatic malignant melanoma was selected for the PICO model discussion from medical educational perspective for both medical students and medical educators. Australia has the highest incidence (men 12% & women 9%) of melanoma in the world with thirty Australians diagnosed with melanoma every day and more than 1,200 death from the disease each year (Understanding Melanoma-Melanoma Institute Australia, 2019) [4]. China has a much lower melanoma incidence rate of 0.17% with approximately eleven Chinese diagnosed with melanoma every day (International Agency for Research on Cancer China Globocan, 2018) [5]. The five equal first authors of this article are interns of the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China. They visited Curtin Medical School, associated teaching hospitals in Perth and general practice clinics for four-week’ supervised electives as medical observers. Their supervisor was the corresponding author and has identified this atypical case of malignant melanoma in general practice clinic for the learning of holistic and comprehensive care from the medical educational perspective. By reviewing the management course of this atypical case of metastatic amelanotic melanoma to brain, the innovative PICO model was used to review the updated treatment of metastatic melanoma with comparing various treatment modalities and the outcomes of treatment. The academic benefit for the Chinese students’ learning is achieved in the management of melanoma, which is a relatively rare skin cancer in China, while management discussion in this case will certainly enrich management options and provide valuable input into future research direction with a relatively common skin cancer in Australia.

Case Presentation

John, a 39-year-old Caucasian man presented to his general practitioner with 2 years history of depression and treated with sertraline (SSRI) with minimal improvement, he also developed chronic low-grade headache for 4 months. In view of his depression and chronic headache, MRI brain was ordered with surprised finding of multiple ring-enhancing lesions with craniotomy biopsy confirming metastatic melanoma, subsequent skin check found an unpigmented mole 2 cm × 2 cm appearing like seborrheic keratosi to be nodular amelanotic melanoma. MDT discussion after review of the literatures indicated the best plan of treatment includes removal of primary lesion and monoclonal antibody treatment with ipilimumab with good effects initially, metastatic lesions reduction in size in 6 months MRI review. The next 3 months’ ongoing treatment did not show any further improvement clinically and radiologically. He simply deteriorated with frequent seizures despite optimal doses of anti-epileptics, and was then referred to palliative care for symptom control and holistic care to ensure good quality of life care. A clinical geneticist was consulted as well for the benefit of his sister and brother in terms of melanoma screening and regular skin cancer check.

Methods and Results

Investigation and methods

In this article, we identify this atypical metastatic malignant melanoma for demonstration of the innovative PICO model for the medical educational purpose of the five Chinese exchange senior medical students. The five students were required to use the innovative PICO model to analyze their daily cases load and identify one case for the daily group debrief with their supervisors. The average case load for each student is eight cases per whole day to apply the innovative PICO model for academic learning. The group has chosen the atypical metastatic melanoma case to demonstrate the PICO-style clinical placement learning.

Salient leaning points and results of group feedback regarding the use of the PICO model

PICO is a relatively new term in both evidence-based medical research and evidence-based medical education in China. The five students have used the innovative PICO model for their daily case studies in symptom analysis, relevant investigation, diagnosis confirmation and treatment modality decision. The feedback from the PICO model use was that it was an excellent and most valuable tool for the busy schedule of clinical placements in hospital and general practice clinics. It has certainly improved the retention of academic knowledge and helped immensely in attaining the clinical reasoning skills to become a competent intern and clinician in future clinical training and practice.

Comparison and outcome with salient points and literature review

In this section of the article, we have used the innovative PICO model to demonstrate the learning of holistic and comprehensive care via evidence-based and individualized approaches by reviewing the management course of this atypical case of metastatic amelanotic melanoma to the brain. We use the opportunity to review the updated treatment of metastatic melanoma with different treatment modalities from different perspectives. Through this case and the innovative PICO model, we have maximized the medical educational benefits for both medical students and medical educators about evidence-based and individualized clinical reasoning with personalized management approach. The perceived benefit will help medical students establish a universally holistic approach in their individual specialty career as a holistically competent clinician. The current concept of holistic approach is defined as optimal patient care in a biological-psychological-social-political-economical-spiritual way.

In the next few sections, we’ll be discussing the different treatment modalities and its literature review on this atypical metastatic melanoma.

Surgery on the primary site of melanoma

Surgical excision with histologically negative margins is the recommended and first-line treatment for primary cutaneous melanoma of any thickness, as well as for melanoma in situ. Surgical margins should be based on tumor thickness [6].

However, as for distant metastatic melanoma, surgery is generally not an option for first-line therapy. For one thing, surgery is rarely curative since the majority of patients with distant metastases have widespread micro-metastatic lesions even if clinical and imaging criteria suggest limited spread. For another, the application of some advanced systemic therapies, such as checkpoint inhibitors, has been proved to be highly effective for patients with metastatic melanoma. Therefore, surgery is mainly performed for limited, isolated soft tissue and nodal metastases that can be completely resected or for complications of metastatic disease in need of urgent palliation (e.g. bleeding or obstructing gastrointestinal lesions).
Surgery is an attractive option for dermal metastases because patients are quickly rendered “disease-free” with relatively limited associated morbidity. In contrast, systemically administered therapies require prolonged treatment courses to achieve relatively inferior local response rates [7]. Besides, excision of systemic, particularly solitary lung melanoma metastases may also increase patient survival [8]. Wong et al. [9] reported a 5-year survival rate of 20% in 144 patients who underwent surgical resection of non-regional melanoma metastases and a phase II trial by the Southwest Oncology Group reported overall 3-year and 4-year survival rates of 36% and 31%, respectively, in stage IV melanoma patients [10].

In the condition of brain metastatic melanoma like what presented in this article, resection is mainly limited to patients with a solitary or single brain metastasis and is often performed for symptomatic relief. Goldinger et al. [11] have demonstrated an overall survival benefit in all patients with single brain metastases who undergo resection compared with radiation therapy alone. There may also be a role for resection in oligometastatic disease of dominant, symptomatic lesions. As the field comes closer to achieving integrated histologic and genetic diagnoses for these patients, a secondary benefit of debulking is the procurement of adequate tumor tissue for molecular characterization. Investigators in one study compared the genomics of matched brain metastases and primary tumors across multiple histologies and demonstrated that >50% of brain metastases harboured genetic alterations that were not detected in the clinically sampled primary tumor [12].

When surgery is considered, careful patient selection is important and treatment must be individualized. Factors to be considered include the severity of symptoms, pace of disease progression, previous treatment and treatment response, patient age and medical condition, and the desires of the patient. Quality of life should be the principal goal of treatment for many patients.

In our case, the brain metastatic lesions are multiple, so resection is not considered as a feasible option. We only performed the removal of the primary lesion with the goal of durable local control as recommended in guidelines [6].

**Target Therapy**

Molecular researches on progression of melanoma have led to drugs targeting specific mutated point of tumor cells.

The largest genomic subtype of melanoma is BRAF V600 mutant which takes up approximately 50% of all advanced melanoma (Cancer Genome Atlas Network, 2015) Vemurafenib and dabrafenib are both potent BRAF inhibitor that significantly improved overall survival for patients with metastatic melanoma harboring BRAF mutant (vemurafenib vs. dacarbazine, OS 13.6 m vs. 9.7 m, P<0.03; dabrafenib vs. dacarbazine, median PFS 5.1 m vs. 2.7 m, P<0.00001) [13]. MEK also plays an important role in pathogenesis of melanoma with BRAF mutant. Trametinib is a highly specific inhibitor of MEK which is proved to significantly prolong PFS in patients with BRAF-mutation positive metastatic melanoma (Trametinib vs. chemotherapy, 4.8 m vs. 1.5 m, P<0.0001). Cobimetinib and Binimetinib are the other two MEK inhibitors approved by the FDA in 2015 and 2018 respectively. Combination of BRAF inhibitor and MEK inhibitor is recommended as first line treatment for metastatic melanoma with BRAF mutation. In 2019, a randomized phase III clinical trial showed that patients receiving dabrafenib plus trametinib achieved PFS rates of 21% at 4 years and 19% at 5 years as well as a complete response rate of 19% [14]. It is a dramatically improvement in patients with BRAF-mutation positive metastatic melanoma.

The other subtypes of metastatic melanoma include NRAS and KIT mutation. Interestingly, binimetinib has shown clinical activity in patients with metastatic melanoma harboring NRAS, who failed to response to immunotherapy. Imatinib is a non-specific c-kit inhibitor, which has also presented with significant clinical responses in patients with KIT alterations. However, these responses are more likely to be seen in tumors harboring KIT alterations of proven functional relevance [15].

Next-generation sequencing has identified our patient as BRAF V600E mutation, which indicates combination treatment of BRAF inhibitor and MEK inhibitor. It is found that β-sitosterol could attenuate melanoma cell growth in vitro and inhibits brain metastasis in vivo, which represented as a promising adjuvant to BRAF inhibitor therapy in patients with, or at risk for, melanoma brain metastasis [16]. Combination targeted therapy plus β-sitosterol can be a reasonable choice.

**Chemotherapy**

Chemotherapy has become a secondary treatment option due to the advances of immunotherapy and targeted therapy. Systemic chemotherapy is considered an alternative therapy only in patients who are not candidates for immunotherapy or target therapy [17].

Dacarbazine, temozolomide, fotemustine and nab-paclitaxel are common single-agent chemotherapy for metastatic melanoma. Dacarbazine and temozolomide are most widely used. Dacarbazine is an intravenous cell cycle nonspecific alkylating agent that is generally well tolerated, with most common side effects of nausea and vomiting. Temozolomide is an orally absorbed analog of dacarbazine. A randomized phase III study showed temozolomide demonstrates equal efficacy to dacarbazine in treating metastatic melanoma [18]. Temozolomide can penetrate the blood-brain barrier due to its lipophilic feature, which presents with better efficacy in patients with brain metastasis of melanoma [19,20]. In 2015, a clinical phase II study showed patients with BRAF mutation and low MGMT expressions had a better response to temozolomide based chemotherapy [21]. Fotemustine is a nitrosourea agent that is considered as a second line chemotherapy after dacarbazine. Given its high lipophilicity, fotemustine also proved its efficacy in cerebral metastasis [22]. Nab-paclitaxel is nanoparticle albumin-bound paclitaxel interfering with disassembly of microtubules to suppress tumor cell proliferation. A randomized controlled phase III trial in 2015 showed that nab-paclitaxel significantly improved PFS compared with dacarbazine in chemotherapy-naive patients with metastatic melanoma (nab-paclitaxel vs. dacarbazine, 4.8 m vs. 2.5 m, P=0.044) [23]. Combination regimens including dacarbazine/temozolomide and carboplatin/paclitaxel are second or third line chemotherapy. There is no evidence to confirm superiority of combination regimens to single-agent chemotherapy.

Chemotherapy did not play a significant role in initial treatment for our patient who had multiple brain metastases with only mild extra cranial cutaneous lesion. However, it could be applied after failure of response to immunotherapy or target therapy. In that situation, temozolomide or fotemustine could be an appropriate option.

**Immunotherapy**

Immunotherapy has become one of the mainstay treatment...
options in an attempt to improve the prognosis of advanced melanoma [24], including special subsets like metastatic brain melanoma [25], mucosal melanoma [26], recurrent female genital tract melanoma [27]. It is critical to determine the timing of onset of immunotherapy, combining radiotherapy with immunotherapy or targeted therapy in metastases [28].

Immune checkpoint inhibitors, such as nivolumab (anti-programmed cell death 1, PD-1), ipilimumab (anti-cytotoxic T lymphocyte-associated antigen 4, CTLA-4), pembrolizumab (anti-PD-1) are monoclonal antibodies approved for treatment of unresectable metastatic melanoma [24]. While combining ipilimumab and nivolumab as first-line regimen, treatment-naive patients with unresectable stage IIIC/IV melanoma achieved higher overall objective response rate than those with failure prior BRAF/MEK targeted therapy [29]. Furthermore, retreatment by nivolumab in challenging subgroups with progressed advanced melanoma on or after ipilimumab displayed safety and effective outcome in phase II clinical trials [30].

Despite of widely used, variant anatomical metastases illustrated different response patterns as well as pseudo-progression and acquired resistance on ipilimumab and nivolumab therapy [31]. Subsequently, a new strategy to realize personalized evaluation of individual patient before initiating anti-PD-1 antibodies is demanding [32]. An updated algorithm, that analyses clinical parameters of tumor linked with the activation rate of CD8+ T cells as well as the net tumor growth rate, is potentially applicable for predicting the progressive time and making better clinical decisions [33].

If received nivolumab-plus-ipilimumab therapy, the patient with brain metastatic melanoma in this case were likely to achieved the progression-free survival of more than 60.0 months. As recently reported, significant immune-related adverse events of immunotherapy include cutaneous and neurocutaneous autoimmune or autoinflammatory diseases, e.g. scleroderma, psoriasis and dermatomyositis [34]. Besides, symptomatic neurologic oedema for brain metastases is a remarkable complication which is a way to focus on in the future [25].

Additional immune-based drugs (cytokine) for metastatic or surgically resected 'high-risk' melanoma, composes of aldesleukin, interferon-a2b, PEGylated interferon-a2b [24]. As another evolving immunotherapy, an oncolytic virus therapy with intra-tumorally administered Talimogene laherparepvec (T-VEC) also shows a benefit in survival of metastatic melanoma, whose mono therapy has been approved in the current National Comprehensive Cancer Network guidelines and combination therapy are undergoing clinical trials [35].

Interestingly, in combination with immune checkpoint therapy, PD-L1 antagonist, Dendritic Cell (DC)-targeted nano-vaccine is promising to boost anti-tumor effects against melanoma in future perspective [36].

Radiotherapy

Melanoma is a tumor relatively resistant to radiation, so it serves mainly as a palliative treatment to the symptomatic metastases to the organs like brain, bone, spinal cord, soft tissues and so on in cases with advanced melanoma as an adjuvant to systemic treatment, as chemotherapy plays a limited role in CNS due to inadequate penetration through the blood-brain barrier. Brain metastases are common in cases with advanced melanoma and are an important cause of death. Surgical removal of masses is effective in symptom control, but there will be a high rate of recurrence [37]. So, for patients with brain metastases, they were treated with surgery followed by whole-brain radiotherapy traditionally to reduce or delay the occurrence of further brain macroscopic diseases. Although advances in radiotherapy techniques like Stereotactic Radio Surgery (SRS) has made great progress in the control of brain metastases adjuvant to systemic treatment, whole-brain radiotherapy is controversial now. As there are new drugs like ipilimumab effective in the brain metastases that cross the blood-brain barrier, and the advent of widespread MRI and screening MRI help discover brain metastases when asymptomatic and small, there’s a greatly reduced need of whole-brain radiotherapy, which has late neurocognitive toxicity, in this radiation-resistant tumor [38]. However, there are also many reports stating that combination of radiotherapy and immunotherapy will lead to a significant improvement in the clinical outcomes, as BRAF inhibitors have radio sensitization effect in melanoma cells [39,40].

Visceral metastases present a better radio sensitivity than brain metastases [41]. However, radiotherapy is not applicable in the intestinal metastases because the intestines move in an irregular way. So the beam could be off-target, making radiotherapy ineffective. In contrast, metastases to the mobile organs like liver and lung can be treated with new techniques like Cyber knife. Besides, fixed foci are amenable to radiotherapy, like the duodenum, para-aortic lymph nodes and adrenal glands [42].

Bone metastases-Radiotherapy is very effective in the symptom control of bone metastases, with a documented rate of up to 96 percent in the long-term pain improvement [43]. For patients with symptomatic bone metastases, Stereotactic Body Radio Therapy (SBRT) may be preferred over External Beam Radio Therapy (EBRT).

Lymph nodes and skin metastases are also common in patients with advanced melanoma [44]. Surgery is the first choice for the cases without extensive distant metastases. But radiotherapy is alternatives if surgery is not feasible. They provide symptomatic control including pain, bleeding and compression of surrounding structures.

As for the choice of total dose and fractions for each patient, there are many documented recommendations for different kind of situations, but each case must be individualized.

Palliative Care Management and Genetic Counseling

Palliative care is an interdisciplinary medical specialty, focusing on symptom management and involving psychosocial, spiritual, ethical, legal support both to patients and their family caregivers. We will focus on symptom management in this article. For advanced melanoma, palliative radiation therapy is an effective method of pain relief except pain-killers for skeletal metastases, cutaneous and lymph node metastases, cerebral melanoma [45]. Besides pain control, treatments of brain oedema and seizure are also important for improving patients’ life quality. Systemic loading-dose glucocorticoids are initially for decreasing brain oedema surrounding metastases and relieving neurologic defects. And then minimum effective dose of steroids for long-term reduces steroid sequelae [46]. If the patient has a seizure, antiepileptic medications are needed. But potential interactions with other anticancer agents should raise doctor’s attention [47].
The etiology of all cancers involves the combined actions between environmental and genetic factor. Ultraviolet exposure is the most significant environmental risk factors for melanoma. Genetic factors, the most common of which are mutations of CDKN2A tumor suppressor gene in familial form of melanoma, also greatly modify the incidence of melanoma. So genetic testing may be indicated for the patients who have individually multiple primary melanomas, or multiple family members with melanoma, coexist with other primary tumors especially pancreatic cancer. However, even in the presence of these criteria, germline mutations in CDKN2A are uncommon, with the prevalence of 1% to 2% [48].

Conclusion and Future Perspectives: Outcome and Outlook

Through this case during the students’ four weeks electives, we have demonstrated our innovative PICO model learning for all the cases. The treatment modality review on metastatic malignant melanoma provides us both a new insight and a deeper understanding into melanoma treatment in future. The perceived benefit will certainly see our medical students adopting a universally holistic approach in their individual specialty career as a competent clinician. The current concept of holistic approach is defined as optimal patient care in a biological-psychological-social-political-economical-spiritual way.

Final Discussion

The PICO model used by the students in this article is innovative and consolidates the students’ learning and increase the retention of academic knowledge and clinical skills, especially in clinical placement setting. It is highly recommended by the authors of this article to introduce this innovative PICO model into the routine undergraduate clinical placement curriculum at both hospital and general practice teaching.

References


