Risk of Incremental Toxicities and Associated Cost of New Anticancer Drugs: A Meta-Analysis

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Disclosure

I have no actual or potential conflict of interest

Introduction

- **New cancer therapies have improved outcomes of people with cancer but they also add toxicities and cost**

- **Improvements in relevant efficacy outcomes with 'acceptable' toxicities observed in registration trials are mostly sufficient for drug approvals**

- **Rare but serious toxicities may not be captured in pivotal clinical trials**

- **Drug regulation process does not consider cost**
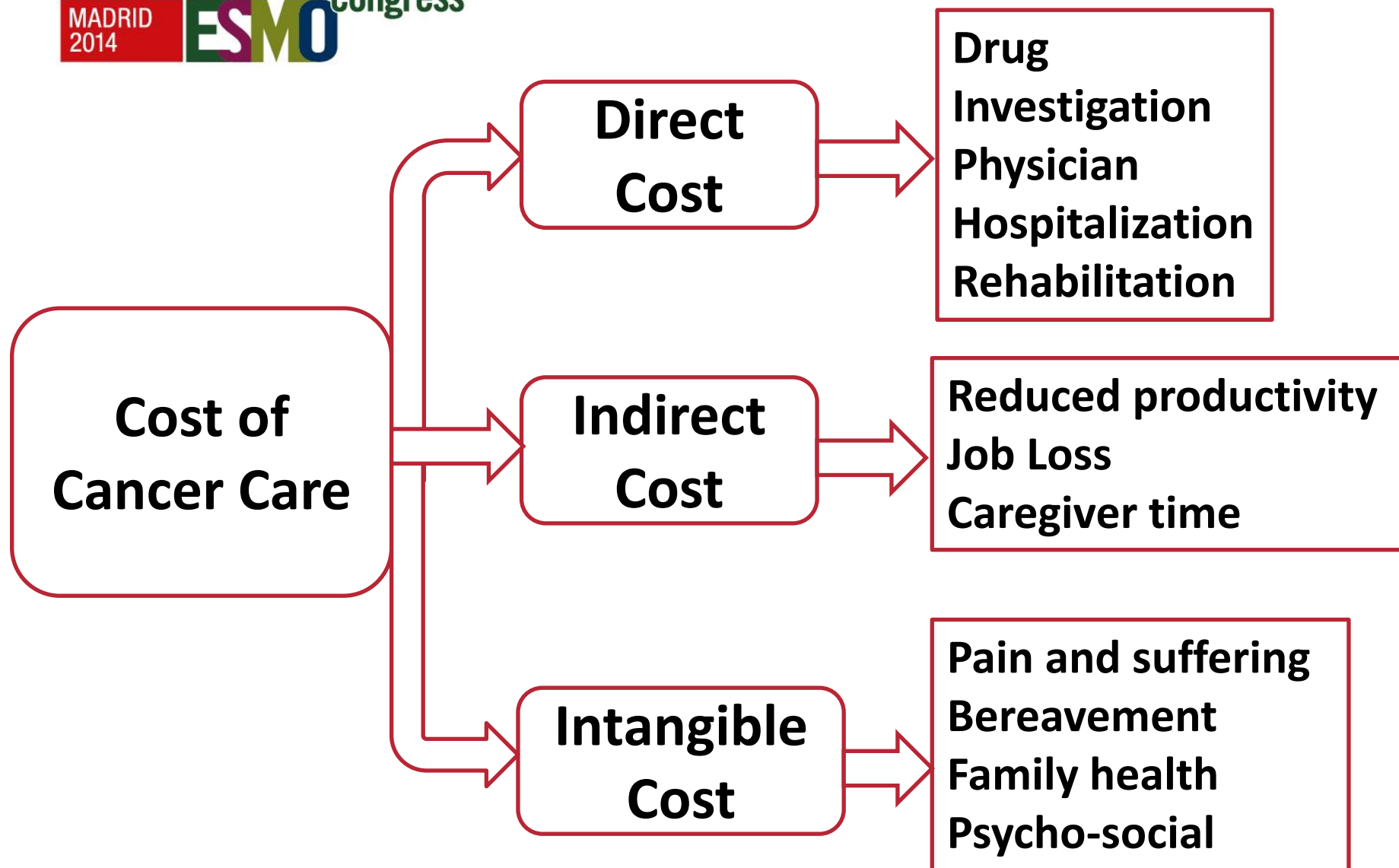
Aims

- **For new anticancer drugs approved by the United States Food and Drug Administration (FDA):**

    I. **To quantify the difference in occurrence of Grade III and IV Adverse Events (AEs) in experimental versus control arms of the pivotal clinical trials**

    II. **To estimate incremental price of new anticancer drugs**

    III. **To estimate the cost of managing incremental toxicities**

Hypotheses

1. **There would be a substantial increment in the price of new anticancer drugs compared to previous standard of care**

2. **New anticancer drugs would be more toxic and therefore would incur higher cost for management of toxicity**

3. **Toxicity and associated costs would differ among the types of new anticancer drugs**

Methods

- **FDA website was assessed to identify newly approved anticancer drugs from 2000 to 2011**

- **Phase III RCTs leading to drug registration for treatment of advanced cancers were identified**

- **Data extraction:**

  - **Frequency of 12 most common grade III or IV AEs were collected from each arms of the RCTs**

  - **Relative Risk (RR) and Absolute Excess Risk (AER) were calculated for the 12 AEs between the arms**

- **RR and AER for each of the 12 AEs were pooled in a meta-analysis using RevMan 5.2**

Sub-groups of new anticancer drugs

I. Specific targeted agents

– **Agents were selected based on a molecular target on cancer cells**

II. Less-specific targeted agents

– **No biomarker was available to guide drug selection, includes angiogenesis inhibitors**

III. Chemotherapy

Sub-groups of included studies

1. **Studies with active anticancer drugs in the control arm**

2. **Studies with either placebo or best supportive care in the control arm**

Methods: Data on Cost

- **Price of anticancer drugs:**

  - **Pharmacy RED BOOK 2011 www.micromedex.com**

- **Cost of toxicity:**

  - **Published data from Medline and Embase**

  - **In case of more than one report on same toxicity, most recent cost used**

  - **Non-US currencies were converted to US$**

- **All costs adjusted for inflation to reflect 2013 US$ value**

PRISMA Diagram

Total unique drug approvals by FDA Jan 2000 to Dec 2011 (n=1,265)

Pivotal trials leading to cancer drug approvals (n=69)

Studies included, n=41 Unique new drugs, n=19 (27,000 patients)

Excluded:
Studies on supportive care (n=18)
Studies with unavailable or unusable data on grade III-IV toxicities (n=4)
Duplicate studies (n=3)
Studies of non-cancer indication (n=3)

12 Most Frequent Toxicities

Adverse events	% of Studies	Adverse Events	% of Studies
Fatigue	88%	Neuropathy	30%
Diarrhea	85%	Erythrodysesthesia	27%
Nausea/Vomiting	82%	Hypertension	27%
Neutropenic Fever	51%	Thromboembolism	20%
Rash	49%	Hemorrhage	20%
Stomatitis	40%	GI perforation	8%

Relative risk of Gr III-IV AEs

Sub-groups (based on drugs)	RR	95% CI	p
Specific targeted agents:	0.7	0.4 to 1.2	0.2
Less specific targeted agents:	3.4	2.2 to 5.1	<0.001
Chemotherapy:	1.7	1.2 o 2.2	<0.001

Sub-groups (based on controls)	RR	95% CI	p
Control group contained active anticancer treatment:	2.1	1.5 to 2.9	<0.001
Control group with placebo/BSC:	3.0	1.6 to 5.7	<0.001

Absolute risk of Gr III-IV AEs

Sub-groups (based on drugs)	AER (%)	95% CI (%)	p
Specific targeted agents	-1.0	-2.2 to 0.4	0.16
Less specific targeted agents	3.0	1.2 to 4.0	<0.01
Chemotherapy	3.0	1.0 to 5.1	<0.01
Sub-groups (based on controls)	**AER (%)**	**95% CI (%)**	**p**
Control group contained active anticancer treatment	3.1	1.7 to 4.4	<0.01
Control group with placebo/BSC	2.4	1.6 to 3.3	<0.01

Incremental Drug Price

	Median (US$) /patient/month	Range (US$) /patient/month
Overall:	**6000**	***-600 to 33,000**
Specific agents:	4,600	-600 to 9,100
Chemotherapy:	5,700	2,800 to 7,800
Less specific agents:	6,700	2,900 to 33,000

*Negative sign denotes experimental agents were cheaper

esmo.org

Incremental Cost of Toxicities

- **Incremental cost of managing AEs was relatively low compared to drug price**

- **Total cost of toxicity was divided among ALL patients in respective arms of the RCTs to get a median per patient 'share' regardless of whether they experienced any AE**

Sub-groups (based on drugs)	Median/ patient (US$)	Range/ Patient (US$)
Specific targeted agents:	*-50	-50 to 35
Less specific targeted agents:	140	15 to 500
Chemotherapy:	275	85 to 740

*Negative sign denotes lower cost in experimental arms

Cost of Toxicities (Range)

- **Specific targeted agents: (Values in US$)**
  - **Minimum: Hemorrhage: -125 (-165 to 150) per patient**
  - **Maximum: Diarrhea: 12 (5 to 85) per patient**

- **Less specific agents:**
  - **Minimum: Stomatitis: 5 (1 to 20) per patient**
  - **Maximum: Neuropathy: 560 (220 to 1355) per patient**

- **Chemotherapy**
  - **Minimum: Hypertension -75 (-100 to 95) per patient**
  - **Maximum: Neuropathy 745 (320 to 1690) per patient**

Limitations

- **We only used published data - toxicities are underreported in published clinical trials**

- **Information on recurring AEs are usually not clear in clinical trial reports**

- **We did not consider low grade AEs**

- **Sources of cost of toxicity were heterogeneous - such cost is sensitive to local healthcare market**

- **Therefore, our data on toxicity are likely to be underestimates of the true cost**

Conclusions

- **Health related and financial consequences of new anticancer drugs are substantial**

- **Specific targeted agents have lower toxicities than control treatments unlike less specific agents and chemotherapy**

- **Less selected patients in the community may suffer from more AEs and cost**

- **Competing social priorities necessitate estimation of economic consequences of new anticancer drugs because resources are finite**

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